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# SAJOUS'S ANALYTIC CYCLOPEDIA OF PRACTICAL MEDICINE

CHARLES E. de M. SAJOUS, M.D., LL.D., Sc.D.  
FOUNDER AND FIRST EDITOR

GEORGE MORRIS PERSOL, B.S., M.D.  
EDITOR-IN-CHIEF  
AND

EDWARD L. BORTZ, A.B., M.D.  
ASSISTANT EDITOR

CHIEF ASSOCIATE EDITORS:

ELDRIDGE L. ELIASON, A.B., M.D.  
*Surgery*

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*Otology, Laryngology, and Rhinology*

L. EMMETT HOLT, JR., M.D.  
*Pediatrics*

FREDERICK H. FALLS, M.S., M.D.  
*Gynecology*

EIGHTH REVISED EDITION

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VOLUME TWENTY-FIVE

SUPPLEMENT



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## PREFACE

**I**N spite of the innumerable difficulties that today beset every editorial effort, it has been possible to prepare a Revision Service Volume for *The Cyclopedia of Medicine, Surgery, and Specialties* covering progress in Medicine and Surgery during the last year. The completeness and excellence of the present volume are a monument to the diligence, interest, and enthusiasm of the fifty-seven contributors who have prepared the various sections. The accomplishment is the more praiseworthy when one considers that, like their professional colleagues, these authors are overwhelmed by the increased amount of work that the present disturbed situation has placed upon them.

This Service Volume, like its predecessors, represents an effort to keep the subscribers to *The Cyclopedia of Medicine, Surgery, and Specialties* abreast of the important advances in Medicine, Surgery, and the various Specialties. The volume does not pretend to be a complete review of current literature. It is rather a series of contributions in which a critical evaluation has been made of the important advances that have taken place in medicine during the past year. Those subjects have been stressed which seemed to be of greatest practical interest to the majority of the medical profession at a time like this.

In this Volume, Anesthesia has been included and special attention has been given to the subject of Caudal Anesthesia. The timely subject of Aviation Medicine has been dealt with somewhat briefly, because, as the author of this contribution pointed out, "much of what is being developed now cannot be published until after the war." The most important aspects of Hematology, from the standpoint of the present worldwide conflict, have been Blood Transfusions, Blood Grouping, and Transfusion Reactions. Therefore much that might be said under Hematology has been omitted in order to stress these few subjects that today command such interest, particularly in our armed forces. The present volume also includes a section on Tropical Medicine. In this, the author has shown a decided tendency to concentrate on Malaria, Yellow Fever, Amebiasis, and those helminthic infections in which recent advances have taken place. Extensive consideration has been given to Plastic and Reconstructive Surgery, as well as Thoracic Surgery. In the section dealing with Therapeutics, special articles devoted to the use of sulfa drugs and penicillin appear. An addition to the volume is a section on Venereal Diseases, with particular reference to the use of the latter drug in Neisserian infections. Aside from the above-mentioned subjects, the book is replete with authoritative articles dealing with many of the phases of disease.

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*General Editor*

W. N. WEECH, M.A., F.S.A.

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# ASSOCIATE EDITORS AND CONTRIBUTORS

---

BERNARD J. ALPERS, M.D.

Professor of Neurology, Jefferson Medical College; Neurologist,  
Jefferson and Pennsylvania Hospitals,

PHILADELPHIA, PA.

(*Neurology and Neurosurgery*)

NINA A. ANDERSON, M.D.

Associate Professor in Pediatrics, Temple University School of Medicine,

PHILADELPHIA, PA.

(*Pediatrics*)

KENNETH E. APPEL, M.D., PH.D., Sc.D.

Assistant Professor of Psychiatry, Graduate School of Medicine, University of Pennsylvania,  
and School of Medicine, University of Pennsylvania,

PHILADELPHIA, PA.

(*Psychiatry*)

CHARLES PHILAMORE BAILEY, M.D., M.Sc., F.A.C.S., F.A.C.C.P.

Lecturer in Thoracic Surgery, Hahnemann Medical College and Hospital; Assistant Clinical Professor  
of Surgery, Women's Medical College and Hospital of Philadelphia; Thoracic Surgeon, Memorial  
Hospital, Wilmington, Del.; Devitt's Camp, Allenwood, Pa.; Episcopal Home for Con-  
sumptives, Chestnut Hill, Pa.; Delaware State Tuberculosis Sanatoria; Brown's

Mills Sanatoria, Assistant Surgeon (Thoracic Surgery), Abington Memorial

Hospital, Roxborough Memorial Hospital, Roxborough, Pa.; Phila-  
delphia General Hospital; Consultant Thoracic Surgeon, Fitkin

Memorial Hospital, Neptune, N. J.; Women's

Homeopathic Hospital,

PHILADELPHIA, PA.

(*Thoracic Surgery*)

ROBERT P. BARDEN, A.B., M.D., D.Sc. (MED.)

Associate in Radiology, University of Pennsylvania Graduate School of Medicine  
and Hospital of the University of Pennsylvania,

PHILADELPHIA, PA.

(*Radiology*)

LOUIS HOPEWELL BAUER, A.B., M.D.

Consultant, Central Islip State Hospital, Pilgrim State Hospital (Brentwood), Kings Park State  
Hospital, Southside Hospital (Bayshore), Mercy Hospital (Hempstead), So. Nassau Communities

Hospital (Rockville Center); Chief Cardiologist, Meadowbrook Hospital (Hempstead);

Attending Cardiologist, Nassau Hospital (Mineola); Consultant to Civil Aeronautics

Administration and to the Committee on Aviation Medicine,

National Research Council,

HEMPSTEAD, N. Y.

(*Aviation Medicine*)

JOSEPH T. BEARDWOOD, JR., M.D.

Associate Professor of Medicine, Graduate School of Medicine, University of Pennsylvania; Physician,  
Presbyterian Hospital; Director of Medical Division, Abington Memorial Hospital; Visiting  
Physician in Charge of Diseases of Metabolism, Bryn Mawr Hospital,

PHILADELPHIA, PA.

(*Diseases of Metabolism*)

## DEACONESS, MAUDE, M.D., M.C.

Director, Department of Ophthalmology,  
 Princeton University,  
 Princeton, New Jersey  
*(Ophthalmology)*

## CONRAD BERENSON, M.D.

Professor of Clinical Ophthalmology, College of Physicians and Surgeons, New York University,  
 and Ear Infirmary, Oculoplastic Ophthalmology, New York University,  
 Internist for Women at Mount Sinai Hospital,  
 New York, New York  
*(Ophthalmology)*

## ALBERT W. BLOOM, M.D., M.C.

Assistant Medical Director, Metropolitan Hospital,  
 New York, New York  
*(Endocrinology)*

## LOUIS H. CHESTNUT, M.D., M.C.

Professor of Laryngology and Bronchology, College of Medicine,  
 Broncho-Pneumonology, Jefferson Medical College, Philadelphia,  
 Visiting Ophthalmologist, Temple University Hospital,  
 Philadelphia, Pennsylvania  
*(Endocrinology)*

## JAMES NORMAN COOMBS, M.D., M.C.

Associate Professor of Pathology, University of Pennsylvania,  
 Philadelphia, Pa.  
*(Endocrinology)*

## JOHN S. COULTER, M.D., M.C., M.A.

Professor and Chairman, Department of Physical Therapy, University of Pennsylvania,  
 Chairman, Committee Physical Therapy, American Medical Association,  
 Physical Therapy, National Research Council, Washington, D.C.,  
 St. Luke's Hospital, Philadelphia, Pa.  
 Chairman, Pa.  
*(Physical Therapy)*

## WILLIAM DAMESIEK, M.D.

Professor of Clinical Medicine, Tufts College Medical School, Boston,  
 Consulting Hematologist, Harvard Medical School,  
 Boston, Mass.  
*(Hematology)*

## CHARLES WILLIAM DUNN, M.D.

Assistant Professor in Medicine, Graduate School of Medicine, University of Pennsylvania,  
 Endocrinologist to Graduate Hospital, University of Pennsylvania,  
 Abington Memorial Hospital, Abington, Pa., (1935-1936),  
 Delaware State Hospital, Maryland, Delaware, (1936-1937),  
 Wilmington, Delaware, The Pennsylvania College of Podiatric Medicine,  
 Philadelphia, Pa.  
*(Endocrinology)*

## FREDERICK H. FALLS, M.D., M.S.

Professor and Head of Department of Obstetrics and Gynecology, University  
of Illinois College of Medicine,  
CHICAGO, ILL.  
(*Gynecology*)

## ARTHUR FIRST, M.D., F.A.C.S.

Assistant Professor of Obstetrics, Jefferson Medical College; Assistant Gynecologist,  
Stetson Hospital; Associate Obstetrician, Mt. Sinai Hospital; Diplomate of the  
American Board of Obstetrics and Gynecology,  
PHILADELPHIA, PA.  
(*Obstetrics*)

## FREDERICK A. FISKE, B.S., M.D., F.A.C.S.

Demonstrator in Surgery, Temple University Hospital; Visiting Surgeon,  
St. Joseph's Hospital and Doctor's Hospital,  
PHILADELPHIA, PA.  
(*Abdominal Surgery*)

## HARRISON F. FLIPPIN, M.D., F.A.C.P.

Associate in Medicine, Schools of Medicine, University of Pennsylvania; Ward Physician,  
Philadelphia General Hospital and Hospital of the University of Pennsylvania,  
PHILADELPHIA, PA.  
(*Therapeutics*)

## SAMUEL B. HADDEN, M.D.

Instructor in Psychiatry, Medical School of the University of Pennsylvania,  
PHILADELPHIA, PA.  
(*Psychiatry*)

## ELMER HESS, M.D.

Chief Urological Department, St. Vincent's Hospital; Senior Urologist, Hornot Hospital;  
Consulting Neurologist, Erie Infants' Home and Corry Hospital,  
ERIE, PA.  
(*Urology*)

## A. R. HOLLENDER, M.D.

Associate Professor of Laryngology, Rhinology, and Otology, University  
of Illinois College of Medicine; Otolaryngologist,  
Research and Educational Hospitals,  
CHICAGO, ILL.  
(*Otorhinolaryngology*)

## G. HENRY KATZ, M.D.

Instructor in Psychiatry, Medical School of the University of Pennsylvania;  
Psychiatrist, Institute of the Pennsylvania Hospital; Psychiatric  
Director, Devereaux Foundation,  
PHILADELPHIA, PA.  
(*Psychiatry*)

## NORMAL KENDALL, M.D.

Instructor in Pediatrics, Temple University School of Medicine.

PHILADELPHIA, PA.

*(Pediatrics)*

## J. J. KOHLHAS, B.S., M.D.

Instructor in Medicine, Schools of Medicine, University of Pennsylvania. Coordinator  
Medical Clinics, Graduate Hospital of the University of Pennsylvania; Assistant  
Visiting Physician, Philadelphia General Hospital; Assistant Physician,  
Outpatient Department, Bryn Mawr Hospital.

PHILADELPHIA, PA.

*(Therapeutics)*

## FRANK W. KONZELMANN, M.D.

Professor of Clinical Pathology, Temple University School of Medicine.

PHILADELPHIA, PA.

*(Clinical Pathology)*

## O. P. LARGE, M.D.

Demonstrator in Surgery at Temple University School of Medicine. Associate Surgeon  
Frankford and Northeastern Hospitals; Consulting Surgeon, Shriner's Hospital.

PHILADELPHIA, PA.

*(Abdominal Surgery)*

## PAUL R. LEBERMAN, LT. (M.C.), U.S.N.R., F.A.C.S.

Chief of Urological Outpatient Department, Hospital of the University of Pennsylvania. Associate  
in Urology, School of Medicine, University of Pennsylvania; American Board of Urology.

American Urological Association; Associate Urologist, Chestnut Hill Hospital;

Assistant Urologist, Jewish Hospital; Consulting Urologist,

State Hospital, Norristown, Pa. On Leave.

PHILADELPHIA, PA.

*(Venereal Diseases)*

## FRANCIS L. LEDERER, COMMANDER (M.C.), U.S.N.R.

Professor and Head of Department of Laryngology, Rhinology and Otology, University of Illinois

College of Medicine, Chicago; Chief of the Otolaryngological Service, Research and

Educational Hospital. On Leave. Chief of Eye, Ear, Nose and Throat

Service, U. S. Naval Hospital,

PHILADELPHIA, PA.

*(Otorhinolaryngology)*

## JOHN B. LUDY, A.B., M.D.

Dermatologist to Episcopal, Pennsylvania, Lankenau, Oncologic, Methodist, and Philadelphia  
General Hospitals; Consultant, Norristown State Hospital and Delaware County Hospital.

PHILADELPHIA, PA.

*(Dermatology)*

## ROBERT A. LYON, M.D.

Associate Professor of Pediatrics, University of Cincinnati College of Medicine;  
Attending Pediatrician, Cincinnati General and the Children's Hospitals.

CINCINNATI, OHIO

*(Pediatrics)*



WILLIAM L. MARTIN, COMMANDER, M.C.V. (G.), U.S.N.R.

Professor of Surgery, Hahnemann Medical College and Hospital,

PHILADELPHIA, PA.

*(War Surgery)*

HANS MAY, M.D., F.A.C.S.

PHILADELPHIA, PA.

*(Plastic and Reconstructive Surgery)*

MERLE M. MILLER, B.S., M.D., F.A.C.P.

Associate in Allergy, Graduate School of Medicine, University of Pennsylvania; Visiting Physician,  
Abington Memorial Hospital; Attending Physician in Charge of Allergic Diseases,  
Bryn Mawr Hospital; Chief of Allergy Service, Germantown,  
Presbyterian and Wills Eye Hospitals,

PHILADELPHIA, PA.

*(Allergy)*

JOHN ROYAL MOORE, M.D.

Professor of Orthopedic Surgery, Temple University School of Medicine;  
Associate in Orthopedics, University of Pennsylvania,

PHILADELPHIA, PA.

*(Orthopedic Surgery)*

EMILY HARTSHORNE MUDD, M.S.W.

Director of Philadelphia Marriage Counsel,

PHILADELPHIA, PA.

*(Psychiatry)*

FRANCIS D. MURPHY, M.D.

Professor of Medicine, Marquette University School of Medicine,

MILWAUKEE, WIS.

*(Diseases of the Kidney)*

WALDO E. NELSON, M.D.

Professor of Pediatrics, Temple University School of Medicine,

PHILADELPHIA, PA.

*(Pediatrics)*

MANUEL M. PEARSON, LT. MC-V(S), U.S.N.R.

Instructor in Psychiatry, Medical School of the University of Pennsylvania,

PHILADELPHIA, PA.

*(Psychiatry)*

RALPH PEMBERTON, M.S., M.D.

Professor of Medicine, Graduate School of Medicine, University of Pennsylvania; Physician  
to Abington Memorial Hospital; Consulting Physician, Chester County Hospital,

PHILADELPHIA, PA.

*(Arthritis and Rheumatoid Conditions)*

## ASSOCIATE EDITORS AND CONTRIBUTORS

EUGENE P. PENDERGRASS, M.D.

Professor of Radiology, University of Pennsylvania Graduate School of Medicine and  
the University of Pennsylvania School of Medicine,

PHILADELPHIA, PA.

*(Radiology)*

DANIEL B. PIERSON, JR., M.D.

Assistant Physician, Medical Service "A," Lankenau Hospital; Assistant Instructor in  
Medicine, Graduate School of University of Pennsylvania,

PHILADELPHIA, PA.

*(Respiratory System)*

CLARE R. RITTERSHOFER, A.M., M.D.

Assistant Professor of Pediatrics, University of Cincinnati College of Medicine.  
Attending Pediatrician, Children's Hospital,

CINCINNATI, OHIO

*(Pediatrics)*

ELIZABETH H. ROSS, M.S.

Secretary of War Service Office—American Association of Psychiatric Workers

PHILADELPHIA, PA.

*(Psychiatry)*

GEORGE P. ROUSE, JR., M.D.

Instructor in Medicine, Graduate School of Medicine, University of Pennsylvania.

Assistant Physician, Presbyterian Hospital; Assistant Physician, Metabolic  
Service, Philadelphia Hospital for Contagious Diseases;

Assistant Physician, Abington Memorial Hospital,

PHILADELPHIA, PA.

*(Diseases of Metabolism)*

HENRY S. RUTH, B.S., M.D.

Professor and Head of the Section of Anesthesiology, Hahnemann Medical College and Hospital;

Chief Anesthetist to Broad Street Hospital; Consulting Anesthetist to

Philadelphia General Hospital,

PHILADELPHIA, PA.

*(Anesthesia)*

WILLIAM G. SAWITZ, M.D.

Assistant Professor of Parasitology, Jefferson Medical College,

PHILADELPHIA, PA.

*(Tropical Medicine)*

C. WESLER SCULL, M.S., Ph.D.

Assistant Professor of Chemistry Assigned to Medicine, University of Pennsylvania

Graduate School of Medicine; Biochemist to Department of Rheumatoid  
Diseases, Abington Memorial Hospital,

PHILADELPHIA, PA.

*(Arthritis and Rheumatoid Conditions)*

## RENDALL R. STRAWBRIDGE, M.D.

Visiting Physician, Lankenau and Abington Hospitals,

PHILADELPHIA, PA.

*(Gastroenterology)*

## LOUIS H. TWYEFFORT, M.D.

Psychiatrist, Institute of the Pennsylvania Hospital; Instructor in Psychiatry,

Medical School of the University of Pennsylvania,

PHILADELPHIA, PA.

*(Psychiatry)*

## JOSEF WARKANY, M.D.

Assistant Professor of Pediatrics, University of Cincinnati College of Medicine;

Fellow, Children's Hospital Research Foundation; Attending Pediatrician,

Pediatric Division, and Attending Physician, Contagious Division,

Cincinnati General Hospital,

CINCINNATI, OHIO

*(Pediatrics)*

## WILLIAM L. WHITE, M.S., M.D.

Fellow, Harrison Department of Research Surgery, School of Medicine, University of Pennsylvania,

PHILADELPHIA, PA.

*(Therapeutics)*

## E. ARTHUR WHITNEY, M.D.

Superintendent, The Elwyn Training School; Instructor in Psychiatry,

Medical School of the University of Pennsylvania,

PHILADELPHIA, PA.

*(Psychiatry)*

## CARROLL SPAULDING WRIGHT, B.S., M.D.

Professor of Dermatology and Syphilology, Temple University School of Medicine;

Associate Professor of Dermatology and Syphilology, Graduate School

of Medicine, University of Pennsylvania,

PHILADELPHIA, PA.

*(Syphilology)*

## H. E. YASKIN, M.D.

Demonstrator in Neurology, Jefferson Medical College,

PHILADELPHIA, PA.

*(Neurology and Neurosurgery)*

## FRANCIS L. ZABOROWSKI, M.D.

Demonstrator in Surgery, Temple University School of Medicine,

PHILADELPHIA, PA.

*(Abdominal Surgery)*

## JOSHUA ZUCKERMAN, B.S., M.D., C.M.

Ophthalmic Surgeon, Midtown Hospital; Assistant Surgeon, Ophthalmology, New York Eye and  
Ear Infirmary; Assistant Attending Physician, New York University College Clinic,

NEW YORK, N. Y.

*(Ophthalmology)*



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# The Cyclopedia of Medicine

Revision Service—1944

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## ALLERGY

MERLE M. MILLER, M.D.

### Allergic Reactions to Injectable Substances

**Yellow Fever Vaccine**—The record of a case of severe constitutional reaction to a single dose of yellow fever vaccine has been reported.<sup>1</sup> It is rare in that it is the only instance of this marked type of reaction in several million immunizing injections which have been given. Sulzberger and Acker<sup>2</sup> have reported three cases of urticaria and erythema multiformelike reactions following the parenteral use of yellow fever vaccine. The entire symptom complex in these cases simulated serum sickness, with arthralgia, malaise, fever, pruritus, nausea, and vomiting.

In the one case reported above the patient was an atopic individual with a multivalent sensitivity with especially marked egg and chicken hypersusceptibility. Yellow fever vaccine was prepared by inoculating eggs incubated seven to 11 days with an attenuated yellow fever virus.

Emphasis was placed on the fact that it is well to obtain a history of allergy before the administration of a vaccine. It is suggested that patients with marked sensitivity to egg or chicken or who react by skin test to yellow fever vaccine should be hyposensitized. It is always important to have *epinephrine* close at hand when administering vaccines or sera to allergic individuals.

**Liver Extract**—Over a period of 12 years about 50 reports of reactions to the parenteral administration of liver extract have appeared in the literature. A few cases have been presented of allergic reactions following the ingestion of liver extract. The total does not exceed seven or eight. The reactions to the injections have been of varying severity from marked local edema to generalized pruritus, urticaria, and angio-neurotic edema.

Some patients have their first reaction after many injections and never have another. Rarely is a reaction encountered after the first dose. It has been the authors'<sup>3</sup> experience that reactions occur most frequently after injections have been stopped for a prolonged period of several weeks to a year. Following a lengthy course of liver extract, a rest period of one month is usually allowed the patient. Care is advised in beginning the subsequent course of injections.

Positive intracutaneous reactions have been elicited following skin testing. Passive transfer has been carried out in quite a few instances. Dilutions up to 1:100,000 have given positive intradermal tests. One case of Crip's was known to give a positive precipitin reaction, but this test was negative when attempted by the author on the patient reported here.

Treatment of the allergic reaction to liver is the same as any other allergic

phenomenon. *Epinephrine*, *ephedrine*, and *calcium* and also *local applications* are indicated. To avoid reaction, the simplest way is to discontinue the liver extract. This is impossible in most cases. Histamine hyposensitization has been suggested, basing the plan on Walzer's belief that some of these reactions are due to histaminelike reactions.

Hyposensitization by gradually increasing doses has been attempted and many claim good results. To begin hyposensitization, dilutions varied all the way from 1:100,000,000 to 1:10. This, it is felt, depends entirely on the degree of sensitivity of each individual patient. Only those patients who react regularly or frequently need to be "desensitized."

Feinberg *et al.*<sup>4</sup> also call attention to the importance and significance of reaction to injectable liver extract. They feel that, considering the number of injections of liver protein, the incidence of reaction is very low but needs to be carefully considered.

There is in many cases an induced allergy which occurs in patients other than primarily atopic individuals. In all instances in this group of patients, reactions followed injections which were previously well tolerated. As in the other series of cases, most reactions followed an interval of three or more weeks in which the patient did not have treatments.

Clinical manifestations were asthma, urticaria, pruritus, and angioneurotic edema. Nausea, weakness, and faintness were common complaints. Anaphylactoid reactions were not encountered in either of these reports but have been described by others.

Elimination or hyposensitization are advised in the treatment of this condition. Specificity seems to be limited to a special fraction of liver not bound with the ordinary protein fraction but with

the antianemic portion. Attention is called to the suggestion that a highly potent antigen containing no protein will sometimes produce skin reaction.

**Insulin Hypersensitivity** An article by Weitz<sup>5</sup> cites a case of hypersensitivity to insulin protein with reactions to direct skin tests and passive transfer. Although the use of insulin in the treatment of diabetes usually causes little difficulty, the fact that insulin produces allergic reaction in some patients has long been recognized. Symptoms, depending on severity of reaction, include mild or marked local discomfort at the site of injection and, in the case of generalized or systemic reactions, marked cutaneous, circulatory, and gastrointestinal manifestations.

Several authors have reported statistics demonstrating an extremely low incidence of diabetes among allergic individuals; conversely, diabetic patients with allergic symptoms are comparatively rare. Despite these findings, however, positive hereditary histories of allergy are frequently encountered among diabetics.

The patient mentioned by Weitz illustrates the similarity between insulin allergy and serum sickness. Reactions to insulin rarely occur following the primary dose, often taking place on the thirteenth or fourteenth day of therapy. Sensitivity frequently occurs following resumption of insulin injections after a lapse of months or even years. This latent period has been compared to the incubation period characteristic of serum sickness.

Desensitization was successfully accomplished in the above patient who proved markedly sensitive to regular beef insulin, moderately positive to protamine zinc insulin and crystalline insulin by intradermal skin test, passive transfer corroborating these findings. Saline control



beef and pork protein gave negative reactions.

**Crystalline insulin** was used for desensitization, the initial dose being 0.1 unit, the amount and interval between doses being gradually increased. After a total of 23 units had been given, generalized urticaria developed, requiring adrenalin for relief. A rest period of 12 hours was followed by varied amounts, slight urticaria occurring occasionally during the next several days. The dosage was finally increased to ten units twice daily with no untoward reaction. Following discharge from the hospital, the amount was decreased to ten units once daily and changes from crystalline to regular beef and pork insulin have incurred no symptoms or reactions. Direct skin tests and passive transfer reactions were all negative.

**Tetanus Toxoid**—The report of a case<sup>6</sup> of anaphylactoid reaction occurring after an injection of plain tetanus toxoid is of interest because of the rarity of such findings in the literature. No symptoms were produced following the first two injections of toxoid but after the third injection the patient's eyes and lips became swollen; he collapsed, and was unconscious for 20 minutes. Sharp, intermittent, epigastric pains followed and persisted for about ten days, necessitating hospitalization. Gastrointestinal studies, physical examination, and laboratory findings were essentially negative. There was no previous history of allergy. Allergic study revealed evidence of positive skin tests, and passive transfer was carried out with corresponding results. The principal findings were positive reactions to four commercial brands of tetanus toxoid as well as to their individual ingredients, the peptone component, the complete toxoid media, beef heart extract, and veal infusion. Evidence cited

points to the veal infusion as the responsible factor.

The advisability of skin tests before the injection of tetanus toxoid is illustrated by the sudden death of a young person, who had not been skin tested, 20 minutes after the injection of a second dose of tetanus toxoid combined with a third dose of typhoid vaccine. Autopsy disclosed the presence of pulmonary edema.

Two cases of sensitivity to fluid tetanus toxoid in atopic individuals are presented.<sup>7</sup> Both show evidence that the toxoid probably precipitated a sensitivity which had existed previously. Both individuals gave no definite history of former allergic manifestations, but following the reactions to the toxoid, studies revealed positive findings by direct skin test and passive transfer. In the first case, marked skin hypersensitivity existed prior to the first injection of tetanus toxoid which caused the reaction. The second case showed marked irritability of the skin following reaction which occurred to a slight degree after the second toxoid injection and markedly following the third. The cases also differed in the duration of symptoms, manifestations in one of whom have persisted for over two years. However, symptomatic improvement has been effected in this case by hyposensitization with fluid tetanus toxoid.

It is emphasized that the incidence of only two cases presenting sensitivity to the toxoid over a period of one year in an institution where daily immunization is given indicates that such manifestations are extremely rare.

The fact that fluid tetanus toxoid and not alum precipitated toxoid was used brings to mind the probability that allergic reactions may be due to the pre-existing proteose sensitivity, since the fluid toxoid does not contain peptone.

### Allergy to Food Odors

The significance of inhalant allergens in relation to infantile eczema (atopic dermatitis) has been reported in the literature. The importance of controlling environmental contactants, such as pollens, house dust, feathers, wool, silk, etc., has been gradually recognized, especially in obstinate cases. Little comment has been made, however, concerning the possibility that food odors may also contribute to the etiology of such dermatoses.

The study of such cases is extremely difficult, because most patients with eczema present a multiple sensitivity. Consequently, it is to be assumed that allergy to food odors occurs more frequently than is indicated in the report of nine cases collected over a period of seven years by Horesh.<sup>8</sup> These cases had all shown marked improvement under previous elimination or desensitization and in each child exacerbations occurred as a direct result of exposure to the offending food vapor. In most instances, the opening of eggs in the presence of the patient was found to be the cause of the flare-up. Chicken, pork, cabbage, and fish also produced similar reactions. In every case, skin tests to the offending protein were positive, 2 to 4 plus, and in every case, proper precautions prevented reoccurrence of the dermatitis.

The author stresses the fact that the majority of patients with eczema are not troubled by sensitivity to food odors and it is probable that this factor is due consideration only in extreme cases. However, allergists have long recognized the fact that foods, as inhalants, can produce allergic symptoms and it is reasonable to offer this as an explanation for refractory cases of infantile eczema.

The writer has seen two cases of marked hypersensitivity to fish odors. One patient always had severe asthma in a restaurant where fish were being fried.

It is possible that the aldehyde fraction of the oil may be a factor.

### Food Allergy and Vitamin C

Holmes<sup>9</sup> presents a subsequent report on the use of vitamin C in the treatment of allergic conditions. His previous paper cited successful results obtained in a group of hay fever patients by the daily administration of from 200 to 500 mg. or more of vitamin C (ascorbic acid) during the pollen season.

The present study included 27 patients and the degree of success was approximately 80 per cent. The allergies of this group consisted of sensitivity to the following: Chocolate, eggs, milk, cheese, wheat, tomatoes, asparagus, potatoes, oranges, lemons, bananas, pork, and fats. Each individual was given 500 mg. of vitamin C daily for one week to the point of saturation, with instructions to decrease the dosage to the minimum maintenance level. Offending foods were eaten at intervals of two or three days while treatment continued.

It is pointed out that two of these patients were allergic to many food proteins but were able to eat practically all foods after taking 200 mg. daily for two or three weeks.

The author calls attention to very occasional evidence of reaction in the form of headache or sore spots around the mouth, and, in one case, diarrhea, after the ingestion of 500 mg. daily despite the prevailing opinion that vitamin C causes no untoward effects even in daily doses of 1000 mg.

### Migraine

Pfeiffer *et al.*<sup>10</sup> review the pertinent factors which combine to make up the migraine syndrome. These might be correlated with changes in blood volume.

1. Onset at puberty and relief at menopause.

2. Greater incidence of migraine in the female.

3. Menstrual migraine probably due to sudden decrease in estrogen.

4. Relief of migraine during pregnancy because of maintenance of high estrogen level.

5. Partial relief of headaches by coal tar and thyroid.

6. Marked relief of headaches by vasoconstrictor drugs such as ergotamine tartrate and benzedrine sulfate.

7. The occurrence of headache after relaxation and fatigue.

The purpose of the study undertaken by the above authors was to determine whether a headache of the migraine type is accompanied by any change in the blood volume. Sex hormones have salt- and water-retaining properties, the estrogens to a greater degree than the androgens. Any sudden reduction in the estrogen level may produce a headache and may be accompanied by changes in blood volume.

Five types of headache are described:

1. Relaxation headache of the business man on Sunday, the day-off headache, and the post-examination headache.

2. Migraine headache in which the patient usually has onesided headache.

3. Menstrual migraine—a dull generalized headache which may occur during the week preceding menstruation or during the first day of the menstrual period. Recovery from the latter is usually much more rapid.

4. Caffeine-withdrawal headaches which follow the withdrawal of caffeine after habitual use.

5. Headaches in the hypertensive patient probably due to an increase in peripheral vascular tone without an equal diminution in effective blood volume.

Relaxation headaches are accompanied by decreased blood volume, the caffeine-withdrawal headache may be due to a

relative increase in the effective arterial blood volume. In migraine there is a relative hemoconcentration but no consistent blood electrolyte changes occur.

The treatment of migraine headache should be directed toward increasing the blood volume or to increasing peripheral vascular tone. The latter can be accomplished by the use of smooth muscle stimulants such as *ergotamine tartrate* and *benzedrine*. The excessive excursion of the cerebral blood vessels is reduced with relief to the patient.

Dreisbach and Pfeiffer,<sup>11</sup> citing the fact that some people ascribe an occasional headache to lack of their morning coffee, have attempted to study and produce such a headache by the withdrawal of the stimulating drug caffeine in habitués. Previously, experimental headaches have been produced by nitrates, histamine, and carbon monoxide. The amount of caffeine used was as high as 0.648 to 0.778 Gm. (10 to 12 gr.) per day. The usual starting dose was 0.130 Gm. (2 gr.). Serum calcium, inorganic phosphorus, potassium, and protein were determined at the height of the headache. Blood specific gravity and hematocrits were also observed.

Oral caffeine is believed to constrict the cerebral vessels and decrease the excursion of the cerebral blood vessels when used in the treatment of migraine. Caffeine is known to dilate the cerebral vessels if given intravenously. It is probable then that the headache produced by the withdrawal of caffeine is due to the direct or reflex dilatations of the cerebral vessels.

The caffeine-withdrawal headache simulates the so-called common headache. This is the explanation, probably, why most medicaments used in the treatment of headache contain caffeine. Headache due to sudden removal of caffeine from the patient's diet has the following char-

acteristics: It is slow in onset, central in origin, and becomes generalized in four to six hours. It is without scotoma and may be accompanied by nausea and vomiting.

In migraine subjects, the headache distinctly differs from their typical migraine attacks. The blood studies showed a lowered serum calcium and elevated serum phosphorus. It is also possible that an increased blood volume accompanies the headache.

The suggestion by Atkinson that there is a possible relationship between Ménière's syndrome and migraine recalls that Ménière himself postulated this in his original paper. Underlying both conditions is a vascular dysfunction. An attempt is made to connect these two entities not only on a mechanistic basis but also from the etiological standpoint.

Allergy may be accepted as a cause of migraine in which primary vasodilation may produce focal edema. There may also be a primary vasospastic disturbance with scotoma and later a secondary vasodilation.

It is possible that Ménière's syndrome and headaches vary only in the difference in location of the "shock organ" for the edema. In one it is in the labyrinth and in the other the cerebral hemisphere.

Allergy as a cause of migraine is common, but as a cause of paroxysmal vertigo is unusual. The former is a condition of youth when vasodilation occurs more readily, the latter in middle life when vasoconstriction more often takes place.

The therapeutic response in both vertigo and migraine gives us important information. In the allergy or vasodilation group, hyposensitization has relieved both the headaches and dizziness. In the vasoconstrictor group which had previously obtained temporary relief by the use of *ergotamine tartrate*, relief was

obtained for many months following the use of *nicotinic acid*. Ergotamine decreases the secondary vasodilation but does nothing to prevent its recurrence. Nicotinic acid prevents the primary fault which is vasoconstriction and, in so doing, secondarily prevents marked vasodilation.

In the use of nicotinic acid, the author does not mean to imply that either Ménière's disease or migraine is a vitamin deficiency. It is only because of the pharmacologic effect of possible vasodilation of central vessels as well as peripheral that this part of the B complex is used therapeutically.

It is felt that there is a close correlation of findings both physiologic and pathologic in Ménière's syndrome and migraine. Always we must keep in mind that each case of either is an individual problem. At times patients will have both vertigo and headache, although often one symptom may be relieved by the onset of the other.

*Histamine hyposensitization* has produced relief in some of the author's cases of migraine. It has been his routine to treat patients either intracutaneously or subcutaneously, preferably the former. The dose is given once or twice weekly and varies from 0.05 to 0.25 cc., depending on the response and reaction of the patient.

### Bronchial Asthma

**Racial Incidence** — Scheppegegrell in 1916 showed, according to statistics compiled by him, that hay fever occurred about one-third as often in negroes as in whites. Hrdlicka found that asthma was rare among the American Indians. Coca had suggested that this allergic trait is not absent in the Indian but much less marked. Derbes and Engelhardt<sup>12</sup> have found that bronchial asthma is not rare in the negro but, in their series of cases,

the incidence of this disease in whites was twice that in the negroes.

It has been the writer's experience that asthma is not an unusual disease among Negroes. He has seen in the past ten years four deaths in Negroes from status asthmaticus. In the above article it has been suggested that Negroes do not have as severe asthma as whites. This has not been the case in his clinics, where Negroes have attacks equally as severe as whites.

**Pathology**—Lamson *et al.*<sup>13</sup> present an extensive report of 86 cases of "fatal asthma" which have been accumulated over a period. It is five years since their previous report. Postmortem examination was done on each individual, the diagnosis of asthma having been made at death. Records were carefully checked to determine the validity of the diagnosis on each patient.

Four children were included in the above series. The authors admit this number is too small to allow many conclusions but point out that they showed absolutely no evidence of "general lymphoid hyperplasia."

Twenty-five adult females were studied, with the following observations:

1. Average age at death was 46.2 years.

2. The duration of dyspnea among those who probably had had asthma ranged from six to 65 years, an average of 19 years.

3. The diagnosis of bronchial asthma seemed possible in only 17 of the 25 cases.

4. Atypical asthma of comparatively short duration may cause many lung changes, while asthma which is typical and of long standing may result in few pulmonary signs.

**Examination** of the 57 male patients reveals the average age at death to be 55 years in contrast to the female aver-

age of 46.2 years, although, in general, the life expectancy of females exceeds that of males. It was also noted that 42 per cent of the males had had asthma at some time previously, the duration averaging 30 years.

Emphasis is placed on the fact that several of the patients in this series died following the use of morphine sulfate, illustrating a definite contraindication for this drug.

An analysis of the pertinent findings showed that bronchial asthma rarely, if ever, causes marked abnormalities of the heart and circulation.

The author of this section has autopsied nine cases of patients dying in status asthmaticus in the past ten years. Except in two cases of advanced years he did not find any evidence grossly or microscopically of cardiac damage. Death in two of these patients followed closely the administration of morphine.

The pathologic findings in Lamson's series were closely simulated by a number of long standing conditions probably preceding the onset of asthma. Interstitial emphysema and multilobular atelectasis were present in one case. Other entities included: (1) Distortion of the thorax, and pressure from without the respiratory and vascular systems; (2) pulmonary fibrosis from tuberculosis or pneumoconiosis; (3) bronchiectasis and bronchostenosis were also found.

Hypertension and syphilitic aortitis with or without aneurysm are diseases which frequently produce asthmaticlike symptoms and signs of true bronchial asthma, and may bring us face to face with a difficult diagnostic problem.

Hilding<sup>14</sup> expresses an opinion that in certain diseases of the lower respiratory tract there is destruction of the cilia and loss of ciliary function which permit the collection of secretions in amounts sufficient to cause death by asphyxia. The

diseases studied include asthma, with and without bronchitis; influenza, and bronchopneumonia. Results definite enough to permit conclusions are evident only in the case of asthma.

The pathologic picture occurring in fatal cases of asthma indicates in many instances a marked change in the bronchial epithelium characterized by a metamorphosis from ciliated columnar to goblet cells without cilia. Although this fact is noted by several others, they have failed to attach to it any degree of significance. It is to be cited that the ciliary system is largely responsible for the removal of secretion under normal conditions. When this mechanism becomes impaired or destroyed, as evidenced by postmortem studies in cases of asthma, the typical viscid mucinous secretion collects in the air passages. Normally, secretions of this type are easily removed by ciliary action, but since this is now impossible, large amounts collect and the patient dies of asphyxia.

The writer suggests as a substitution for ciliary action the *mechanical removal of secretion*. This could be accomplished by *bronchoscopy* or *tracheotomy* and would serve as a temporary measure until the ciliated cells can be restored. Replacement of these cells in the nose following acute rhinitis has been proved to be very rapid. It can therefore be assumed that the same results would occur in the lower respiratory tract.

### Nethamine Hydrochloride and Theophylline Isobutanolamine

A study of 250 cases of nasal allergy and asthma is presented by Hansel<sup>15</sup> in an attempt to evaluate the relative efficacy of *nethamine hydrochloride* and *theophylline isobutanolamine* in the treatment of such cases.

The value of *ephedrine* in allergic therapy has long been known but its tendency to produce symptoms of nervousness, palpitation, headache, nausea, etc., has occasioned the development of several compounds. The one considered in this study is nethamine (brand of methylethylamine - phenylpropanol) hydrochloride, also known as 1-N-ethyl-ephedrine hydrochloride. Pharmacological studies on this preparation show it to be as effective as ephedrine in the rôle of bronchodilator and respiratory stimulator. It has been well tolerated in the patients sensitive to ephedrine and adrenalin.

A new soluble theophylline derivative, theophylline isobutanolamine, has been studied pharmacologically and the following conclusions drawn: It is a stable compound, containing approximately 67 per cent theophylline and demonstrating actions characteristic of theophylline. Experiments on rabbits have proved that it is comparatively nontoxic and less toxic than some of the other soluble theophylline derivatives.

The merits of theophylline preparations in the treatment of asthma have been described by many observers. Their value in patients who have become adrenalin-fast has been emphasized and it is interesting to note that its use in many instances has apparently in some way overcome previous refractoriness to adrenalin. Untoward effects from its use have been slight and easily controlled except in a few cases.

Recent reports give encouraging results obtained from the use of aminophylline rectal suppositories, as well as in the usual oral, intramuscular, and intravenous methods of administration.

The majority of patients observed in this study presented nasal symptoms with their asthma, consequently they were treated with a combination of nethamine,



0.046 Gm. ( $\frac{3}{4}$  gr.), and theophylline isobutanolamine, 0.130 Gm. (2 gr.). Nasal symptoms usually improved along with the relief of asthma.

Results obtained in this series correspond with the observations of others concerning the theophylline compounds and can be summarized as follows: **Theophylline isobutanolamine** is an effective drug producing prompt relief due to its rapid absorption. Unpleasant effects occur rarely and repeated administration does not necessitate increased dosage.

### Inhalation

Lockey<sup>16</sup> presents a method for the relief of asthmatic attacks by the inhalation of **oxygen** and **1:100 epinephrine hydrochloride** plus 5 per cent **glycerin**. For many years relief of severe asthmatic paroxysms has been effected by the inhalation of a 1:100 solution of epinephrine hydrochloride, usually by means of a fine spray produced with a hand bulb vaporizer. This method has been improved upon by a simple technic of providing continuous inhalation through the use of a pressure tank of oxygen, a valve regulating the flow. The resulting advantages of this procedure include lessening of exertion on the part of the patient, the absorption of a greater amount of solution, and the efficacy of milder bronchodilator drugs.

Untoward effects from the use of either the hand bulb vaporizer or the continuous inhalation method have been noted as dryness and irritation of the throat, palpitation, nervousness, weakness, nausea, headache, and dizziness. In an effort to overcome these disadvantages, the author has incorporated 5 per cent glycerin into the 1:100 epinephrine solution. Comparison of results obtained in two groups indicate that irritation and dryness of the throat occurred 82 per

cent less often among asthmatics using glycerinated 1:100 epinephrine hydrochloride.

The technic for making the glycerinated solution appears below:

<i>Suprarenalin</i>			
<i>crystals</i> .....	10	Gm.	(150 gr.)
<i>Sodium chloride</i> ..	9	Gm.	(135 gr.)
<i>Chlorobutanol</i> ....	5	Gm.	(75 gr.)
<i>Sodium bisulfite</i> ..	0.9	Gm.	(14 gr.)
<i>Dilute HCL (10%</i>			
<i>U. S. P.)</i> .....	20	cc.	(5½ fl. dr.)
<i>Glycerin</i> .....	50	cc.	(13¾ fl. dr.)
<i>Distilled water to</i>			
<i>make</i> .....	1000	cc.	(34 fl. oz.)

Triple distilled water, 850 cc., and glycerin, 50 cc., are heated to boiling to remove the dissolved air. The heat is shut off and the chlorobutanol and sodium chloride are added. The solution is cooled to room temperature and the sodium bisulfite is added. Ten grams of suprarenalin crystals are dissolved in 20 cc. of 10 per cent HCl and added immediately to the above solution. The pH is then adjusted to 3.0 (a fluctuation from 2.9 to 3.1 is permissible). If necessary, a few drops of dilute sodium hydroxide may be used to bring the pH to 3.0. Distilled water is added until the volume is exactly 1000 cc. The solution is then filtered and bottled. Metal apparatus is to be avoided in the preparation of this solution.

### Poison Ivy

Ellis,<sup>17</sup> in a report on the present status of prophylactic treatment of poison ivy, concludes that the use of extracts of **poison ivy antigen** in tablet form may be a more practical and convenient method of administration than by injection. Widely varied reports in the literature indicate that oral administration or the injection of the antigen are of little or no value in the prevention of poison ivy. Reports of successful desensitization have been based mainly on clinical im-

provement, since little, if any, decrease in patch test sensitivity has been demonstrated. Comparison of results obtained by various investigators is difficult because the potency of poison ivy extracts is not standardized.

The oral method of prophylaxis is often accompanied by a persistent pruritus ani and general itching. The author suggests, however, that short rest periods be given when annoying symptoms occur and that the dosage be gradually increased. Indication that there is an increase in tolerance is evidenced by the gradual lessening of anal or generalized itching. Production of a decrease in patch test sensitivity indicative of clinical immunity requires the ingestion of large amounts of the extract and necessitates a course of treatment extending over many months. These factors are not conducive to cooperation on the part of patients except in the case of those subject to severely disabling attacks. One patient was gradually immunized after the total ingestion of 13,000 mg. of poison ivy extract in tablet form, extending over a period of approximately six months.

The use of the oral method has proved of no therapeutic value in attacks of poison ivy dermatitis. A dosage of less than 1 mg. per day will often produce generalized reaction at the beginning. It is wiser to start with a dosage of 0.05 mg. daily.

**Poison Ivy in the Army**—Clinical reports from 32 stations in the Fourth Service Command on the use of a 5 per cent *alcoholic extract of poison ivy leaves* in the treatment of dermatitis venenata show encouraging results.<sup>18</sup> Of 2544 patients diagnosed as dermatitis due to poison ivy, 1851 were treated with the extract and results tabulated classify 68 per cent of these as good and 18.4 per cent as fair.

In an attempt to prevent disability, either partial or complete, due to poison ivy, various methods have been employed with little success. In most training camps, it is difficult to exercise any control over contact with poison ivy. The use of local applications of creams or lotions has proved of little value. Elimination of the weeds locally is a time- and labor-consuming process.

The extract used in this study was a 5 per cent alcoholic extract of poison ivy leaves prepared at the Fourth Service Command Laboratory according to the method of Cooke and Spain. The number of injections necessary for control of symptoms ranged from two to six, and the average length of hospitalization necessary for severe cases was substantially reduced. At no time was there evidence of constitutional reactions with the exception of local soreness and swelling. Of the 1851 patients treated with the alcoholic extract, 86.4 per cent obtained satisfactory or fairly satisfactory results. One thousand, seven hundred and forty-eight did not miss a day of duty due to their dermatitis.

### Army Allergy

The majority of reports in the literature concerning allergy as related to the social and economic status of the patient would seem to indicate slight evidence from which to assume such a relationship exists. In an effort to study this subject, the Boston Recruiting and Induction Station reports on the examinations of 60,000 selectees, an excellent sample of the male population of military age from all walks of life.<sup>19</sup> Of this group, total rejections for general military service were 21,500, 495 of which were disqualified due to allergy. The rejected cases were classified according to communities from which they came, all of which were studied socially as to



the following categories: Social economic state, nationality, welfare, occupation, housing, and density. Several factors, such as the prevalence of air-borne allergens, the consumption of highly antigenic foods, the hereditary background, etc., have necessarily been overlooked in the explanation of the results obtained. However, the following conclusions indicate a definite variation in the incidence of allergy with regard to diversified conditions: The highest total rejection rate occurred in crowded tenement districts, lowest in one-family residential areas, and was comparatively high in semirural communities. There was no significant variation in the rejection rate for neuro-circulatory asthenia which was chosen as a control. Findings in the above study suggest a lower incidence of allergy in the poor.

A discussion of the military aspects of allergy points out the growing need for an organized department of allergy in the Army. The problem has recently become more acute due to the drafting of 1B individuals who, in many instances, can be successfully used by the Army despite their minor physical disabilities. It is estimated that over 1 per cent of all soldiers entering the Armed Service require allergic care, and the organization of an allergy department would ensure the treatment of these men and their assignment to places and duties where they will be of most value.

It is also demonstrated that the problem of allergy confronting the Army includes, in addition to the above, the professional duties of the Army allergist and the formulation of specific physical standards for all allergic diseases.

Blank<sup>20</sup> feels that the allergist is of greatest value at the training centers where he is able adequately to observe and diagnose the patient. He should possess thorough knowledge of allergic fac-

tors to be encountered in various locations and under all circumstances which will enable him to reclassify soldiers for noncombatant duty if necessary and, in intractable cases, to discharge men who would present therapeutic problems. The ability of the allergist to estimate the capabilities of each soldier is of prime importance. The services of the Army allergist should also be utilized in conjunction with the dermatologic, ophthalmologic, and otorhinolaryngologic sections. It is also suggested that the allergist should supervise all serum and vaccine therapy.

Plans for organizing an allergy department include the formation of a board of allergists whose duties would consist of the collection and distribution of all pertinent data and the standardization of all methods and supplies used in the allergy department and the establishment of allergy sections at training centers and general hospitals for the prognosis, classification, and treatment of allergic cases.

The rôle of the allergist in military medicine is assuming increased importance due largely to the relaxation of restrictions by Selective Service in order to fill its quotas. This situation necessitates proper treatment of the allergic soldier so that he may be used by the Army in his most efficient capacity.

French and Halpin<sup>21</sup> report on the results obtained by the Allergy Section established in the Fourth Corps Area in March, 1942. Fifty-nine clinics have now been organized and are supplied with standardized materials for testing and treatment obtained at a very low cost due to centralization of preparation. The problem of training personnel for this service was met by the institution of a short intensive course in allergic investigation and therapy. The simplification of methods and supplies has contributed greatly to the successful maintenance of

the clinics by previously inexperienced medical officers.

A total of 3917 patients was seen in 21 of the clinics reporting in this survey. Respiratory infections comprised the largest number of complaints. Hospitalization was necessary in 1153 cases, 71 per cent of which were attributable to bronchial asthma. The average number of hospital days was 18.1.

The fact that 267 patients were reclassified and considered suitable for limited service in contrast to 195 discharged for disability indicates the advantages of proper supervision of the allergic soldier and the assured significance of the allergist in military medicine today.

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## ANESTHESIA

*Edited by* HENRY S. RUTH, M.D.

### PREANESTHETIC SEDATION

**Demerol**—This drug has been assuming some importance in the current literature as a preanesthetic medicament for the past few years. Chemically, it is ethyl-1-methyl-4-phenyl-piperidine-4-carboxylate, and employed as the hydrochloride. It is readily soluble in water, has a neutral reaction, and a slightly bitter taste. A solution of this drug is not decomposed by a short period of boiling.

Demerol hydrochloride exhibits a spasmolytic action and also rather pronounced analgesic properties. It has a relaxing action on the smooth muscle of the intestinal tract, the uterus, the bronchial tree, and the urinary bladder. Its analgesic action has been estimated between that of morphine and codeine.

Administered preoperatively, demerol exhibits a desirable sedative effect upon the patient and removes much of the fear of the surgical procedure. Rovenstine and Batterman<sup>1</sup> claim that it is a satisfactory substitute for *morphine* or other opiates in this respect. They reported its clinical use in 338 patients, and a footnote to the report calls attention to the fact that another 600 patients had received the drug. Of importance as a preanesthetic sedative drug, demerol exhibits both atropine- and morphine-like activities. When *ether*, *cyclopropane*, *divinyl ether*, and *nitrous oxide* were employed, it was satisfactory in producing psychic sedation, facilitating the induction of anesthesia, and reducing the amount of the inhalation anesthetic agent required.

Some believe that it is superior to morphine in drying secretions and exhibits fewer of the undesirable side-effects of nausea, vertigo, and respiratory depression. The dosage suggested is 100 mg. for most patients below 60 years of age and 75 mg. for older patients. Fifty mg. is generally considered inadequate. Demerol may also be employed in combination with *scopolamine* in the ratio of 0.6 mg. with 100 mg. of demerol and 0.5 mg. with 75 mg. of demerol. This suggested optimal time for administering the demerol-scopolamine combination is 45 to 90 minutes prior to the administration of anesthesia. The results of demerol alone and combined with scopolamine are very similar.

**Nembutal and Scopolamine**—Hawk and Wangeman<sup>2</sup> have recommended the combined use of nembutal and scopolamine for preanesthetic sedation. Nembutal, given alone in doses of 0.194 Gm. (3 gr.) to subjects previously tested with morphine and morphine plus scopolamine, did not exhibit a depressant effect. Respiration was slightly increased and minute volume respiration decreased approximately 10 per cent. When 0.00065 Gm. ( $\frac{1}{100}$  gr.) of scopolamine was administered with the nembutal, respiratory function was increased still further, as was the minute volume respiration and oxygen consumption. The combination of scopolamine and nembutal produced a longer-acting but less profound and more potent sedation than nembutal alone, in spite of an increased restlessness shown by patients. This combination is recommended for preoperative sedation and for the inhibition of mucus, but it does not serve as an agent for the relief of pain, and consequently must be supplemented near the end of operation by some analgesic drug.

**Atropine and Scopolamine**—These drugs were compared by studies on nor-

mal adults by Wangeman and Hawk.<sup>3</sup> The most pronounced effects of atropine were exhibited on the circulatory system. Both drugs *decreased* the depression of minute volume respiration produced by *morphine*, but scopolamine exerted a greater effect in this respect than did atropine. Scopolamine was shown also to be twice as effective in producing a drying effect and a psychic depression. The authors conclude that a combination of *morphine and scopolamine* in a ratio of 25:1 produced a more satisfactory effect than any single drug or any other combination of drugs.

Anderson and Essex<sup>4</sup> studied the effect of *morphine sulfate*, *atropine sulfate*, and *pentobarbital sodium* employed separately or in various combinations as preanesthetic sedative drugs to animals in ether anesthesia. Traumatic shock was induced by intestinal manipulation, and the tendency toward shock was noted by studying the hemoconcentration, blood pressure, etc. They came to the conclusion that morphine sulfate, in doses comparable to those administered to human beings, did not delay the onset of shock or death in animals under ether anesthesia, when compared to like situations without its use. Atropine sulfate proved to be the most effective agent in delaying the onset of shock and death in these animals, particularly when atropine sulfate was the only drug employed. The efficiency of atropine sulfate appeared to be reduced when it was combined with morphine sulfate or pentobarbital sodium, or even both of these drugs. Pentobarbital sodium in the dosage used was also effective in delaying the onset of shock and death in animals under ether anesthesia but to a lesser degree than atropine sulfate. When morphine sulfate was combined with atropine sulfate or pentobarbital sodium or both, the morphine appeared to decrease

the effectiveness of the other drugs in delaying the onset of shock and death in these animals.

## INHALATION ANESTHESIA

**Ether—*Ether Anesthesia and Pulmonary Tuberculosis***—Beecher and Adams<sup>5</sup> have expressed their opinion that the current prejudice concerning the use of ether anesthesia in the presence of tuberculosis does not appear to be based on evidence. They therefore employed ether anesthesia with the carbon dioxide absorption technic in operations on consecutive patients undergoing surgical treatment for pulmonary tuberculosis. In a clinical study, covering a period of five years during which 260 operations were performed on 147 patients, ether was used and they conclude that the results compared favorably with those from other institutions where ether was rarely used or considered contraindicated. They compared the rate of mortality and arrest of disease in their own series and found them to be near the average of six groups of cases treated by others. They conclude that ether is the anesthetic of choice in tuberculous patients because they believe that ether administered by the closed system provides no increase in hazard to the tuberculous process, permits great freedom of action to the surgeon, and institutes a depression of vagal activity so important in thoracic surgery.

**Use of Bulk Ether in Anesthesia**—Gold<sup>6</sup> is under the impression that the safety of bulk ether for surgical anesthesia appears to be established. Attention has been called to the fact that ether to be used for anesthesia must be preserved in tight containers of capacity not more than 3 Kg. Therefore, it is illegal to ship ether labeled "for anesthesia" in containers which hold more than that

amount. Exigencies of the war have special significance to restrictions and savings. It is, therefore, interesting to know that ether U. S. P. may be shipped in containers of any size provided they are labeled "ether not for anesthesia," or, if desired, "ether U. S. P. not for anesthesia."

On the other hand, Rovenstine and Papper<sup>7</sup> believe that it seems advisable to avoid the use of ether that is suspected of containing impurities. The National Board of Fire Underwriters points out that if proper safeguards for handling bulk ether are employed, it may also be more economical to purchase ether in the small containers. At the Bellevue Hospital in New York City, the cost of ether per case has been reduced to approximately seven cents while maintaining the use of ether in small containers. Such a reduction in cost was accomplished by reorganizing the anesthesia service on a professional basis. The authors conclude that "for convenience and the priceless confidence in his drug, the anesthetist would prefer to open a small container of ether, administer anesthesia for the day, and discard the unused portion."

**Chloroform**—Crawford<sup>8</sup> has reported delayed chloroform poisoning in five patients, all of whom had been in labor for a long time, with frequent vomiting, so that they were dehydrated, acidotic, and uremic when the anesthetic was given. The postpartum condition was characterized by vomiting, jaundice, abdominal pain, fever, tenderness over the liver, and the presence of bile pigment in the urine which occurred on the third postpartum day. These patients were treated with *continuous intravenous infusions of 50 per cent glucose* with the concentration gradually reduced to 5 per cent, *intravenous saline*, and small doses of *insulin with glucose*.

Crawford believes that a crisis occurs between the fourth and fifth days in delayed chloroform poisoning, and that if a patient does not succumb at the end of five days recovery may be anticipated.

**Cyclopropane**—Cardiac arrhythmias have received much study and attention both experimentally and clinically.<sup>9</sup> It has been shown in dogs receiving cyclopropane that cardiac irregularities developed spontaneously at about the level of respiratory arrest. These irregularities were not associated with hypoxemia, and were increased in frequency and severity with an increase in concentration of the cyclopropane inhaled. It appears to be the consensus that arrhythmia is a warning signal which indicates a reduction in the concentration of the anesthetic agent or a change to another anesthetic agent, rather than an increase in the concentration of cyclopropane. In experiments on dogs, the administration of 22 per cent cyclopropane in oxygen, without the addition of ether, led to marked sensitization of the heart to **epinephrine**, as judged by the production of tachycardia when the epinephrine was injected. In dogs, cardiac irregularities could not regularly be prevented by the administration of **sodium amytal**. On the other hand, a mixture containing 22 per cent cyclopropane in oxygen plus 4.5 per cent diethyl ether was found effective for maintaining deep surgical anesthesia without sensitizing the heart to epinephrine. Another advantage of this latter mixture containing ether was that it did not depress respiratory function as much as did cyclopropane in oxygen alone. The two mixtures behaved similarly with regard to speed of induction and recovery, moment-to-moment control, and abdominal relaxation. Experimenting with cats, employing a mixture of 20 per cent cyclopropane and 4.5 per cent diethyl ether in oxygen, the

depth of anesthesia was similar to that obtained with 30 per cent cyclopropane in oxygen, and the cardiac arrhythmias were less severe than those produced with 20 per cent cyclopropane in oxygen. It appears to be increasingly recognized that a mixture of cyclopropane and oxygen with *minimal* amounts of ethyl ether may be preferred to either cyclopropane or ether alone, in view of the fact that the combination retains the speed of induction and of recovery which characterizes cyclopropane, and it has the added advantage of stimulating respiration and giving more complete abdominal relaxation, as well as decreasing the tendency toward cardiac arrhythmia.

Patients under cyclopropane anesthesia rather uniformly show a displacement of the acid-base equilibrium toward an acidosis,<sup>10</sup> due to accumulation of carbon dioxide. This effect can be alleviated by: (1) eliminating the dead space in the mask and canister; or (2) controlling artificially the rate and depth of respiration by restoring minute volume respiration to or above the patient's normal level.

The work of Hershey and Rovenstine<sup>11</sup> has tended to support the clinical observation that cyclopropane is a useful anesthetic agent in the presence of circulatory depression due to recent, extensive hemorrhage.

**Vinyl Ether**—In a report authorized by the Council on Dental Therapeutics of the American Dental Association,<sup>12</sup> it has been suggested that it is advisable to confine the use of vinyl ether in dental practice to persons well trained in the administration of dental anesthetic agents. Attention is called to the fact that vinyl ether is more potent than nitrous oxide. The explosion hazard is about the same as that of ethyl ether. Vinyl ether is definitely contraindicated in patients with diseases of the

liver, and is not the drug of choice in high altitudes.

### INHALATION TECHNIC

The closed carbon dioxide absorption technic of inhalation anesthesia requires the use of a substance which is effective for the absorption of carbon dioxide from such closed systems.<sup>13</sup> Mixtures of sodium and calcium hydroxide, known as soda lime, from the standpoint of cheapness have heretofore been found most practical and were in general clinical use. Recently mixtures containing *barium and calcium hydroxide* have been tried for absorption, and the preliminary trials offer considerable promise of their being effective. The barium-lime mixture, prepared in the form of pellets, has a greater degree of hardness and is comparatively free of dust. Its absorbent nature toward carbon dioxide can be favorably compared with soda lime. It has been noted that the absorptive efficiency of the barium-lime mixture remains high until the charge nears complete exhaustion. Temperatures generated by the absorption of carbon dioxide by soda lime are slightly higher than those of the barium-lime mixture.

An indicator-type soda lime has been introduced which, when no longer capable of absorbing carbon dioxide from expired mixtures, is said to have shown a change in color. Tests on this indicator type soda lime, by means of a mechanical "lung," show that the indicator type was as efficient an absorber as the ordinary type soda lime of the same granule size, moisture content, and alkali content. However, it was also demonstrated that the indicator color and point were unreliable, and that the transparent canister necessary for observing the color change deteriorated rapidly. Conroy and Seevers<sup>14</sup> believe

that the only criterion of inadequate carbon dioxide absorption should be based on physiological evidence.

### REGIONAL ANESTHESIA

#### Continuous Caudal Anesthesia

In the last two years, continuous caudal anesthesia has assumed some popularity in its application to obstetrics. The method was originated and developed by Hingson and Edwards,<sup>15, 16</sup> and has been applied by them to many hundreds of cases, as well as by others. Although the use of continuous caudal anesthesia for obstetrics is based on a sound premise, at the same time it must be pointed out that certain difficulties may be encountered and that it may be accompanied by potential dangers and complications. Some writers claim that a thorough experience in sacral caudal block is necessary for the safe application of this type of anesthesia to the pregnant woman.

**Equipment**—A special malleable needle devised by Edwards is advocated, which is so designed that breakage at the hub is minimized. A length of rigid rubber tubing of narrow caliber with the necessary adapters connects the needle, after it is in place, to a 10 cc. syringe. If preferred, a valve may be inserted between the rubber tubing and the syringe which, in turn, is connected to another length of the rubber tubing which is attached to a container holding the local anesthetic solution. All the above parts may be assembled so that the local anesthetic solution may be aspirated into the syringe from the container and injected at will into the caudal space.

#### Method of Hingson and Edwards

—The patient is placed either in the knee-chest, knee-elbow, or laterally flexed position. After the usual skin preparation and draping with sterile towels the



needle is inserted into the caudal canal for a distance between one to two inches. A preliminary aspiration test is then done by attaching the syringe to the needle, and making negative pressure in order to observe whether or not spinal fluid or blood may be aspirated. The position of the needle must be changed in the event the aspiration test shows a positive reaction. If the aspiration test is negative, 6 cc. of a 1.5 per cent solution of *metycaine* may be injected, followed by a waiting period of ten minutes. This will determine whether or not spinal anesthesia has been obtained. After the anesthetist has been certain that the needle is in the caudal canal and that it is extradural, the procedure may be continued. All the parts of the apparatus are assembled and an additional dose of 30 cc. of the 1.5 per cent solution of metycaine is injected during an interval of no less than two minutes. Subsequent doses of the anesthetic solution average 20 cc. of the same concentration of the same drug injected every 30 to 40 minutes. The needle is fixed into position by means of cotton or a piece of sterile felt and adhesive tape.

Preparation for continuous caudal anesthesia may be begun when the first stage of labor has definitely been established. Satisfactory analgesia may be evidenced by flushing of the toes and feet within 5 to 15 minutes of the initial injection. The addition of a vasoconstrictor may or may not be employed; in the majority of Hingson and Edwards' series none was added. Subsequent doses may be given as stated above every half hour, 40 minutes, or as indicated by the experiences of the mother. It has been said that anesthesia may be safely prolonged for an indefinite period. Continuous anesthesia for 13 hours has been recorded. Usually there is no alarming fall in blood pressure and the babies are

born in vigorous condition. The method has been advocated as providing complete perineal relaxation; low forceps may be applied where required. It is further stated that there is little tendency to moulding of the fetal head for the cervix dilates rapidly. The force of the uterine contractions is not appreciably affected, providing anesthesia of undue height is not instituted (10T).

**Contraindications** — Infection over the site of injection precludes its use. Anatomic anomalies or excessive obesity may obviate the introduction of the needle. A dural sac abnormally prolonged into the sacral canal may make it impossible to place the needle in the correct position without aspirating spinal fluid. Advanced anemia and psychic disorders, as well as idiosyncrasies to cocaine or its derivatives, may also be listed as contraindications to the method.

Additional contraindications recorded include placenta previa, uterine inertia, maternal hysterical or psychotic conditions, and disproportion between the fetus and the maternal pelvis.

**Complications**—Occasionally, a drop greater than 20 mm. of mercury in systolic blood pressure may occur. Increased nausea and vomiting have occasionally been noted. There have been reports of needles broken *in situ* which require surgical removal. Infections have developed at the site of injection. Neurological sequelae are apparently rare, but have occurred. Severe collapse and death may occur if an overdose of the anesthetic agent is injected intraspinally. If an intravenous injection be made, a toxic local anesthetic reaction will usually follow quickly if the dose injected into the venous system has been large. Unilateral anesthesia may develop if the point of the needle is directed laterally, to a great degree, and a complete or

partial fibrous septum is present in the caudal canal.

**Catheter Method**—Following the usual preparation with the patient in the Sims position or knee-chest position, an intradermal wheal is raised over the sacral hiatus, and 5 cc. of the local anesthetic solution is introduced through the sacrococcygeal ligament by means of a 50-mm. needle.<sup>17</sup> A 13-gage Love-Barker needle with stilet in place is introduced through the sacrococcygeal ligament with the bevel posterior, at an angle of 45°. This position is maintained until it impinges on the anterior wall of the sacral canal, when it is turned so that it may be advanced upward into the canal. A number 5 ureteral catheter is threaded through the needle into the canal until its tip rests at the level of the second sacral foramen, when the needle is withdrawn, leaving the catheter in place. The anesthetic solution now is introduced *slowly* in order to avoid pain, headache, nausea, and the usual reactions from injection of a solution under too much pressure in the epidural space of the caudal region. The ureteral catheter is strapped to the patient's buttocks; this permits the patient to turn to any position without producing trauma. Subsequent injections are introduced in manner similar to the needle technic of Hingson and Edwards.

### Refrigeration Anesthesia

Anesthesia by means of the proper application of cold has produced encouraging success, particularly in the lower extremities. The procedure is begun at varying intervals, depending on the level of the amputation contemplated. If a mid thigh amputation is to be done, the cold is applied 3 hours pre-operatively; for amputations about the knee, 2½ hours; and for lower leg amputations, 2 hours' preparation is ade-

quate. Indication is made by staining the skin at (1) the amputation line, (2) the saw line, (3) the tourniquet line (three to six inches proximal to the line of incision). If infection is present, merely bandaging the leg with an ordinary gauze bandage is adequate. If no infection is present, the extremity is elevated and an Esmarch bandage wound about it, beginning at the level of the toes and continuing to a point above the level of amputation. At the level of the tourniquet (previously demarcated), three ice bags are placed so that they will surround the leg for an interval of one-half hour. The Esmarch bandage is then unwound down to the tourniquet line and a tourniquet is applied. The tourniquet should consist of gummed rubber ½ inch in width, tightly clamped from three to six inches above the line of amputation. A second tourniquet of the same material is superimposed directly upon the first tourniquet and clamped in similar fashion. Rubber sheeting is placed on the bed underneath the extremity. On the rubber sheet, a layer of ice of two to three inches in thickness is arranged, beginning at a level below the foot and extending from two to three inches *proximal* to the tourniquet. The leg is then placed upon this bed of ice. Ice is packed around the entire leg; that is, in contact with all its surfaces, for a depth of from two to three inches. The rubber sheet is then folded over this layer of ice and clamped so that it will retain its position. The head of the bed is raised and the lower end of the rubber sheeting is arranged as a funnel which drains into a bucket; this procedure will drain off the melted ice and maintain the bed in a dry condition. If the amputation contemplated is to be performed below the knee, the patient may be placed in a sitting position and the leg involved



plunged into an ice bucket. The ice is not to be removed until the patient is on the operating table. At that time the ice and the rubber sheeting are removed, the limb dried without rubbing, prepared in the usual manner, and the operation begun. Chilled, sterile saline should be employed for irrigation and for moistening gauze tampons. The tourniquet is moved only when the wound is ready to be closed. No drain is used if any infection is present. Silk sutures are preferable. The resulting anesthesia usually lasts about one hour. Preliminary sedation may be employed only if the patient is unduly apprehensive. As an extra precaution, a screen may be placed in position so that the patient cannot observe the operation, and the ears may be plugged with cotton to shut out auditory disturbances. Postoperatively, ice bags should be placed on the stump for an interval between 48 to 72 hours.

### SPINAL ANESTHESIA

A fall in blood pressure is an accepted possibility whenever high spinal anesthesia is instituted. Papper and his associates list six theories which have been evolved to explain its occurrence. They are (1) hematogenous intoxication, (2) direct action on the medulla, (3) paralysis of the adrenal nerves with reduced secretion of epinephrine, (4) hypoxic theory, (5) paralysis of the vasoconstrictor fibers in the anterior spinal roots, (6) theory of stagnation in the postarteriolar bed. Studies were instituted by them on patients undergoing high spinal anesthesia on whom an operation was performed, and contrasted with the effects of spinal anesthesia on the blood pressure of normal patients in the supine position who were not given premedication or experienced surgery. Less than one-fourth of the patients who

were not operated upon showed a fall in blood pressure, whereas three-quarters of the clinical patients exhibited hypotension. The authors noted that the hypotension occurred after the surgical manipulations had been begun in practically every instance. Therefore, the authors believe that the normal patient is competent from the viewpoint of circulation to handle his circulatory needs in a resting state in a supine position, even though undergoing spinal anesthesia to the sixth thoracic vertebra or above. On the other hand, patients under the effects of spinal anesthesia of the same height undergoing trauma coincidental with operative manipulation may undergo a marked reduction in blood pressure, and if the trauma is severe enough, a complete circulatory collapse may occur.

They believe that the selection of patients is most important in order to prognosticate fall in blood pressure during high spinal anesthesia. Patients whose cardiovascular system has been disturbed preoperatively do not respond well to further embarrassment engendered by the spinal anesthesia. Papper and his associates believe that the treatment of hypotension should be directed toward increasing the venous return to the heart, maintaining adequate cardiac output, and increasing the oxygen tension of partially unsaturated arterial and venous blood. They therefore advocate inhalations of oxygen and the use of the pressor drugs. *Ephedrine* is their choice of the vasoconstrictor drugs because it causes an elevation of the blood pressure by increasing the venous return and by increasing the right auricular venous pressure, as well as the cardiac output.

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## ARTHRITIS AND RHEUMATOID CONDITIONS

RALPH PEMBERTON, M.S., M.D., AND C. WESLER SCULL, Ph.D.

### Arthritis in the Armed Services

The relative importance of arthritic conditions in the armed services is shown by data compiled by Boland.<sup>1</sup> During 1942 nearly 11 per cent of admissions to the medical service and 41 per cent of admissions to the general medical section of the Hoff General Hospital were for complaints referable to the joints and muscles. It should be observed that the cases reaching general hospitals are screened and the overall incidence in the army is considerably less than suggested by the aforementioned figures. Rheumatic complaints in the army present several problems which differ in some respects from those encountered in civilian practice. Boland describes 350 cases, 214 of which presented disturbances in the peripheral joints, and 136 of which presented dis-

turbances in the back. A difficulty of accurate differential diagnosis is not infrequently encountered in cases seen early in the course of rheumatic fever, rheumatoid arthritis, and gonococcal arthritis. The comparative incidence of several varieties is shown by the occurrence of psychogenic rheumatism in 44; rheumatoid arthritis in 41; osteoarthritis in 35; acute rheumatic fever in 34; unclassified arthritis in 30; fibrositis in 10; gonorrheal arthritis in 10; gout in 3; and miscellaneous varieties, hemophilic, psoriatic, ankylostomiasis, etc., in 12 cases.

Rheumatoid arthritis in this series appears more acutely and less frequently in the joints of the fingers than is generally seen in civilian practice. In 70 per cent of the cases the disorder affected the lower extremities. Although not

certain, it appears likely that this is related to decreased resistance established by minor joint trauma.

Gonorrheal arthritis in certain stages can be differentiated only with difficulty from rheumatoid arthritis. Because of the stigma attached to the diagnosis of gonorrheal arthritis, such a description is applied only when proved conclusively by positive identification of the gonococcus in the and/or clear cut association with Neisserian urethritis.

Osteoarthritis as encountered in the army is similar in all respects to that in civilian practice, differing only in respect to lower incidence which is due to the lower age of the army personnel.

Fibrositis appeared much less frequently in Boland's cases (4.7 per cent) than among those reported by British physicians among the British Expeditionary Forces (70 per cent). According to Boland, this is due to the inclusion of what he classes as psychogenic rheumatism by the British.

**Psychogenic Rheumatism**—Psychogenic rheumatism was found to be the most frequent cause of disability in 450 consecutive cases diagnosed as arthritis or an allied organic condition previous to admission to the medical service of Hoff General Hospital by Boland and Corr.<sup>2</sup>

By the term "psychogenic rheumatism" is meant states in which symptoms such as pain, stiffness, subjective sense of swelling, or limitation of motion in the muscles or joints are caused, intensified, or perpetuated by mental influences. When disability results from such a state in the complete absence of structural joint or muscle abnormalities, the condition is designated as "pure psychogenic rheumatism." When incapacitating psychogenic symptoms are associated with nondisabling organic changes, the psychogenic rheumatism is considered to be "superimposed."

From this group, 50 cases of psychogenic rheumatism were studied in some detail. Twenty-eight of the 50 patients had no objective evidence of muscle or joint disease and were regarded as examples of pure psychogenic rheumatism. Eighteen had minor nondisabling structural changes, and four patients had a persistence of an incapacity after all physical manifestations of an observed organic process had completely subsided. The incidence of psychogenic rheumatism in enlisted men seems to be unrelated to age, rank, previous occupation, intelligence, or education. Thirty-eight patients gave a history of peripheral joint or back symptoms prior to entry into military service. Twenty patients, or over one-third of the series, gave a history of invalidism or semi-invalidism from rheumatism in one or more members of their immediate families.

The sites of election for symptom fixation were predominantly the back and lower extremities. The majority of patients had definite psychoneurotic manifestations before entry into military service. Forty-six of the 50 patients had definite associated psychoneurotic symptoms in addition to the rheumatic complaints.

In the peripheral group, the most frequent symptoms were pain, stiffness, limitation of motion, subjective sense of swelling, and weakness of the involved part.

By far the outstanding characteristic in the patients with psychogenic backache was the persistence of the disability in spite of prolonged bed rest. Continuous night and day discomfort, refractory to bed rest and physical therapy, and augmented by slight physical exertion, was typical.

The diagnosis of psychogenic rheumatism is facilitated by the recognition of

certain points at the time of examination or during the period of observation. These include (1) gross incongruities between the quality or severity of the symptoms and the structural changes; (2) persistence of the disability; (3) qualitative functional characteristics of the presenting complaint; (4) bizarre postures or limps; and (5) the association of other hysterical or psychoneurotic manifestations.

Attempts to salvage these patients with psychogenic rheumatism and to return them to either full or limited duty have been largely unsuccessful. In many instances, the only solution rests in the removal of the underlying mental conflict which can be accomplished by separating them from military service. In others, the underlying emotional make-up is so poor and the associated psychoneurotic manifestations are so definite that rehabilitation for military service would be neither feasible nor advisable.

### Pathology

**Rheumatic Fever and Rheumatoid Arthritis**—Bennett<sup>3</sup> reported findings in 150 surgically treated and 48 and 101 autopsied cases of rheumatoid arthritis and rheumatic fever subjects, respectively. Some degree of rheumatic carditis was found in all the 101 autopsied cases, and the Aschoff nodule was found in 67 instances. Of the remaining cases, 29 showed myocardial cicatrices, probably healed Aschoff nodules. Macroscopic changes indicating old or recent pericarditis or both were present in 70. In 33 instances, there was either complete or nearly complete obliteration of the pericardial space. Extrapericardial adhesions were found in 40.

Although exudative and proliferative changes in the articular tissues of rheumatic fever subjects have been described

by others, their incidence in the present series was small.

Post-mortem examinations of 49 rheumatoid subjects revealed that the most constant and significant pathological changes are confined to the skeletal system. Inflammatory lesions characterized by hyperemia and a marked diffuse lymphocytic and plasma cell infiltration of the subsynovial tissues, frequently accompanied by the formation of lymphoid follicles, were the earliest alterations noted.

It is of interest that in both rheumatic fever and rheumatoid arthritis, subcutaneous nodules appear in approximately 20 per cent of the cases. It is concluded that the usual anatomical changes observed in rheumatoid arthritis differ so markedly from those of rheumatic fever that the pathogenesis of the observed lesions is different. Therefore, in the absence of etiological evidence to the contrary, it would seem advisable to continue to look upon rheumatic fever and rheumatoid arthritis as separate and distinct entities.

**Rheumatic Heart Disease in Rheumatoid Arthritis**—Of 23 autopsied cases of rheumatoid arthritis, Bayles<sup>4</sup> found six had changes in both the heart valve leaflets and the myocardium similar to those that usually follow rheumatic fever. Excluding one patient because of definite rheumatic fever and rheumatic heart disease in childhood, 22 per cent had rheumatic cardiac lesions. No patient who had histologic evidence of rheumatic fever failed to show evidence of this on gross examination. A coincidence, a relationship between rheumatic fever and rheumatoid arthritis or the possibility that the heart disease is related to rheumatoid arthritis, might be inferred from these data. In the clinical treatment of these patients, Bayles preferred to consider the cardiac

changes a coincidence of rheumatic heart disease and rheumatoid arthritis.

**Cause of Death in Rheumatoid Arthritis**—Rosenberg, *et al.*,<sup>5</sup> report 30 autopsied cases of rheumatoid arthritis. In each case the arthritis had been progressive and had produced some degree of crippling. The articular changes were easily detected and included spindle-shaped swellings of joints, atrophy of muscles, synovial thickening and effusions, and some degree of fibrous ankylosis. In a few early cases, roentgenograms were negative, but in most of the cases the roentgenograms showed swellings of soft tissues, osteoporosis, varying degrees of destruction of cartilage and bone, narrowing of joint spaces, and sometimes marginal lipping. Constitutional reactions were commonly present.

The causes of death can be classified into three groups. In the first group, the fatalities were not in any way related to the arthritis, deaths being due to coronary occlusion, pulmonary suppuration, accidental death, and death from carcinoma. In the second group, deaths resulted from some form of therapy undertaken for the arthritis; for example, deaths from reactions to typhoid vaccine, from cinchophen hepatitis, fat embolism following manipulations of joints, and pulmonary embolism following applications of casts. In the third group, the deaths appear to have resulted from visceral diseases which probably represented a part of the rheumatoid disease; for example, rheumatic heart disease, amyloid degeneration, or prolonged exhausting diarrhea.

### Clinical Pathology

**Surface Film Produced by Blood Plasma from Arthritic Patients**—Scull and Pemberton<sup>6</sup> describe a semi-quantitative technic for the production and study of films on the surface of

water from small amounts (1 cu. mm.) of blood serum and plasma. Differences have been observed with respect to the areas of films produced by equivalent volumes of normal and pathologic specimens. The areas of film formed by blood fluids from patients with rheumatic disorders are frequently smaller than those produced by blood fluids of normal subjects. One cu. mm. of normal plasma produced films with areas of 550 sq. cm., whereas the same quantity of plasma from certain severely ill atrophic arthritic patients produced films ranging from 150 to 450 sq. cm. Films produced by plasma from less acutely ill arthritic subjects attained more nearly normal areas. These data show that the rheumatic patient suffers from a disorder of the physicochemical pattern of his blood as well as from a pathologic process in his joints.

While these deviations apparently bear a general relation to the degree of systemic involvement, they should not be regarded as pathognomonic for arthritic diseases. Some evidence is presented indicating the probability that a major factor determining the magnitude of the films relates to variations in the concentration of proteins in the specimens studies. Full interpretation of the observed differences requires more data than are now available, but there are reasonable grounds for the speculative view that certain physiologic consequences must follow upon a reduction in the "film-forming stuff" in body fluids of arthritic subjects.

**Rheumatoid Spondylitis as a Cause of Increased Cerebrospinal Fluid Protein**—Ludwig, *et al.*,<sup>7</sup> examined the cerebrospinal fluids obtained from 101 patients with rheumatoid arthritis, 59 of whom suffered from peripheral joint disease alone and 42 from spondylitis with or without peripheral joint

involvement. The only significant abnormalities observed were increased total protein, abnormal colloidal gold curves, or a combination of the two. The fact that 15 of the 16 patients with increased spinal fluid protein had either spondylitis or symptoms suggesting spinal involvement strongly suggests a relationship between an elevation of the spinal fluid protein and the presence of rheumatoid arthritis in the spinal and sacroiliac articulations. Such alterations occurred more frequently in the spondylitis patients with severe pain or sciatica or both and hence presumably a higher degree of inflammatory activity. Factors probably involved in the production of these abnormalities are alterations in the serum proteins and increased permeability of the meninges because of their proximity to the inflamed articular tissue.

### Endocrine Factors

**Experimental Arthritis** — Selye, *et al.*,<sup>8</sup> have produced an experimental rheumatic syndrome in rats which simulates the histologic pattern of rheumatoid arthritis and rheumatic fever in man. The development of this experimental syndrome was accelerated by exposure to cold, a factor which has often been prominent in precipitation of the clinical condition. Adrenalectomy and thyroidectomy were also found to increase susceptibility to the development of rheumatic lesions in animals receiving desoxycorticosterone acetate.

The rheumatic syndrome was produced by the subcutaneous injection of desoxycorticosterone acetate twice daily for a period of 14 to 26 days in rats sensitized by the removal of one kidney. Sodium chloride was included at a level of 1 per cent in the drinking water of the animals. In some of the animals the thyroid was removed; in others, the

adrenals were removed. In these subjects, signs of arthritis appeared on the fourteenth day in the form of swelling in the tarsal joints of the hind feet, together with occasional swelling in other joints. On autopsy nephrosclerosis, periarteritis nodosa, and rheumatic nodules in the heart were macroscopically evident. Microscopically, the acute cases presented edema of the periarthicular connective tissues and synovial villousities, with hydrarthrosis. In advanced cases, the mesothelial lining of the synovials showed distention, necrosis, and hyalinization. Fibroid necrosis is also found in tendon sheaths and subcutaneous tissues in the periarticular regions. Granulation tissue develops around the hyaline fibrinoid deposits. In more advanced cases, the edema subsides and the granulomatous tissue becomes quite dense. In the region of the periosteum, this stimulates formation of new bone. These changes are suggestive of hypertrophic lesions, although the articular cartilage was not visibly affected in any of the joints.

While exposure to cold, thyroidectomy, adrenalectomy, and the ingestion of sodium chloride accelerated these pathologic changes, desoxycorticosterone acetate alone produced rheumatic lesions in some animals. In view of the clinical and histologic similarity of symptoms in these animals to those in rheumatic fever, Selye believes that rheumatic fever is a manifestation of adrenal cortex hyperactivity. It is further pointed out that stresses other than exposure to cold are capable of inducing adrenal-cortical hyperactivity.

### Central Factor

**Clinical Considerations** — The experimental syndrome produced in rats by Selye, *et al.*, indicates that the adrenal cortex may play an important rôle in



the pathogenesis of rheumatic fever and rheumatoid arthritis. Together with the previously reported studies of Silberberg regarding the influence of pituitary extracts on the production of joint lesions suggestive of osteoarthritis, they provide sound experimental bases for a more active study of the rôle of endocrinous factors in the pathogenesis of rheumatic diseases in man. Some of the implications in this direction have been outlined by Pemberton and Scull<sup>9</sup> in the table on pages 26 and 27.

In summarizing, Pemberton and Scull suggest that the symptoms of rheumatic diseases can be interpreted as direct consequences of disturbance in the several functions of the neuroendocrine system as a whole. These disturbances may be determined either by congenital inadequacy or by excessive stimulation with subsequent periods of functional hyperactivity or hypoactivity. It appears unlikely that any single factor is responsible for producing the full pattern in any case. The exacerbation of symptoms of stiffness and pain in an arthritic during the premenstrual phase of the reproductive cycle, and the remission of rheumatic complaints during pregnancy, although more immediately referable to gonadal activities, involve pituitary activities as well. Similarly, arthralgic manifestations associated with hypothyroidism may involve other endocrine factors. States of fatigue and general asthenia characterizing many chronic arthritics could be attributed to adrenocortical insufficiency secondary to dysfunction of the pituitary. Circulatory and thermoregulatory disturbances, seen in many arthritics and involving imbalance of the nervous system, may likewise depend upon endocrine influences.

These considerations, in addition to their theoretical interest in accounting for the symmetrical distribution of le-

sions and certain systemic dysfunctions, bear suggestive therapeutic corollaries which have not yet been fully explored and invite clinical as well as experimental exploitation. Nothing approaching finality of detail is here implied or intended but it is abundantly clear that any attempt at visualization of the arthritic problem as a whole must include in its purview the broad outline of some of these considerations.

### Etiology

**Nutritional Background**—A detailed study of the dietary histories of 31 patients with rheumatoid arthritis has been made by Bayles, *et al.*<sup>10</sup> The survey covered the entire dietary habits of the patient from childhood to the day prior to admission. While such a procedure could not be expected to provide quantitative data for the diets of the earlier years, it was believed that some trends might be revealed. For the more recent dietary supplies, the calories, protein, carbohydrate, fat, iron, calcium, vitamins A, B, C, and G were calculated on the basis of average servings.

Except for four patients who lost weight the caloric supply was adequate. The supply of protein was in excess of the minimum of 44 grams per day, although nine patients secured less than the minimum suggested by the N. R. C. In only six patients were the carbohydrates in excess of 50 per cent of the calories. Fats were used in amounts comparable to those of the population in general. While no gross deficiency of supply of iron was encountered, seven patients received less than the allowance recommended by the N. R. C. The supply of calcium was found to be less than the recommended allowances, although this is a common situation and not peculiar to the arthritic group.

POSSIBLE RÔLE OF PRECIPITATING FACTORS, ACTING SINGLY OR IN COMBINATION, IN PRODUCING  
SYMPTOMS OF CHRONIC RHEUMATIC DISORDERS THROUGH THE  
MEDIATION OF "CENTRAL FACTORS"

Precipitating or Sustaining Factors	Affecting Relative Functional Levels of Neuro-Endocrine System	Symptom Complex Resulting in the Arthritis	Type of Arthritis Involved
Infection, toxemia, hereditary imbalance, physiological "draft"; "starvation"; vitamin B complex deficiency	<i>Hypo</i> function of the <i>adrenotropic</i> factor of the pituitary or	Increased susceptibility to infection, toxins, histamine	A & H
	Adrenal cortex	Caries	A & H
		Fatigue	A & H
		Asthenia	A
		Hypotension	A
		Low BMR	A & H
	<i>Hypo</i> function of the <i>growth</i> factor of the pituitary	Asthenic (small stature)	A
		Secondary anemia	
		Decreasing capacity for protein synthesis	A & H
		Demineralization	A
Menopause	<i>Hyper</i> function of the <i>growth</i> factor of the pituitary	Osteophytes	H
		Calcification of cartilage	H
		Acral enlargement	H
		Paresthesia	
		Megacolon	H
		Sthenic (large stature)	H
	<i>Hypo</i> function of the <i>thyrotropic</i> factor of the pituitary or	"Dry" skin	H
	Thyroid	Low BMR	A & H
	<i>Hyper</i> function of the <i>thyrotropic</i> factor of the pituitary or	High BMR	
	Thyroid		
	<i>Hypo</i> function of the <i>gonadotropic</i> factor of the pituitary or	Arthralgia	A & H
	the gonads	"Flashes"	
		Fatigue	
		Sweating	
		Vasomotor	
		Emotional instability	
		Headache	
		Hypertension	



POSSIBLE RÔLE OF PRECIPITATING FACTORS, ACTING SINGLY OR IN COMBINATION, IN PRODUCING  
SYMPTOMS OF CHRONIC RHEUMATIC DISORDERS THROUGH THE  
MEDIATION OF "CENTRAL FACTORS"

Precipitating or Sustaining Factors	Affecting Relative Functional Levels of Neuro-Endocrine System	Symptom Complex Resulting in the Arthritic	Type of Arthritis Involved
Pregnancy	<i>Hyper</i> function of the <i>gonadotropic</i> factor of the pituitary or  Gonads	Relief of symptoms	A
	<i>Hypo</i> -vasopressor factor of the posterior pituitary  <i>Hyper</i> -vasopressor factor of the posterior pituitary	Decreased peristalsis Low blood pressure  Water retention Edema Decreased skin capillary flow	A & H
	<i>Nervous System</i>		
Mechanical pressure by capsular distention, bony overgrowth, tissue swelling	Pain fibers	Pain	A & H
Nervous stress or strain from: worry, excessive activity, exposure to cold—trauma	Vegetative nervous system  (1) Stimulation followed by (2) Exhaustion  (a) Increased adrenergic response (Epinephrine)  (b) Increased cholinergic response (Acetylcholine)	Peripheral vasoconstrictions Hyperglycemia Relaxation gastrointestinal tract  Increased gastrointestinal tone Flushing Palpitation Sweating—general	A & H
Exhaustion	Decreased adrenergic response	Reduced resistance to fatigue—cold Decreased BMR Poor regulation body temperature	A

The survey as a whole indicates that the dietary history before onset of rheumatoid arthritis is not grossly different from that of families of the North Atlantic states. However, two-thirds of the patients fell short of the recommendations of the N. R. C. for calcium, thiamine, and riboflavin; one-half had inadequate supplies of ascorbic acid and a few were insufficiently supplied with protein, iron, or vitamin A.

It is believed by these investigators that the nutritive disturbances in arthritics are due to increased demands created by work, worry, and fatigue, rather than to a primary deficiency of supply.

**Food Allergy in Subacute Recurrent Arthritis**—In a consecutive series of 1000 adults complaining primarily of allergy (asthma, hay fever, urticaria, migraine, and allergic dermatitis, and indigestion), Vaughn<sup>11</sup> found that 27 had recurrent subacute involvement of various joints. The allergic etiology in these 27 cases was indicated either by the fact that the causative foods were discovered and the attacks prevented by their avoidance, or that, although the etiologic foods were not discovered, the joint manifestations appeared synchronously with other allergic symptoms and were relieved with improvement in the latter. Thirty-two foods were incriminated. Strawberry and tomato, the "hearsay" foods customarily suspected in rheumatism, were relatively unimportant in this list. Although food allergy has not been proved to play a part in the majority of arthritics, there appears to be a small group in whom intermittent hydroarthrosis involving large joints or multiple small joints (with a picture of recurrent subacute rheumatoid arthritis) may be caused by food allergens. This may occur in persons whose joints are normal between attacks or may appear as an exacerbation in persons with

chronic arthritis, presumably not caused primarily by food allergy.

## Treatment

### Recent Advances in Treatment

In a survey of the field of rheumatic diseases, Slocumb and Polley<sup>12</sup> reach the conclusion that the ultimate cause of rheumatoid arthritis remains unknown. While inclined toward the belief that rheumatic fever and rheumatoid arthritis are distinct syndromes, they recognize that there are still differences of opinion regarding the relationship of the pathologic features of these conditions. Treatment is regarded as consisting of: (1) Help for the patient to improve his general resistance; (2) proper care of the joints, muscles, and fibrous tissue to minimize damage in the joints, deformities, contractures, and muscle atrophy; and (3) temporary control of the active rheumatoid arthritis in the hope that it will give the patient an opportunity to build up sufficient resistance to control the disease after the treatment has been discontinued.

In respect to these, *rest* is regarded as essential. *Systemic rest* as well as *local rest for the afflicted joints* is indicated. Cautious use of *salicylates* is considered appropriate as a means for promoting rest. *Mild sedatives* but not opiates are regarded as indicated for the same purpose. An optimistic but realistic attitude on the part of the physician is considered as contributory to the *essential mental rest* for the patient. *Well balanced dietary measures*, together with *control of focal infection*, are useful not as specifics but as valuable supportive procedures.

Individualized *orthopedic, physical therapeutic*, and *occupational therapeutic measures* constitute the basic elements in care for the joints, muscles, and tendons.

The profession, having already discarded many so-called specific measures in the treatment of rheumatoid arthritis, is advised by Slocumb and Polley to put high dosage with *vitamin D* in its proper place, *viz.*, as an agent to be tried cautiously and then only as a supplement to programs for patients in whom conservative measures are inadequate. Toxic manifestations should be expected and the use of vitamin D alone is not justified. Similar considerations are applicable to the use of *gold salts*. These agents are toxic and should not be given until after one to three months of conservative treatment.

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## DERMATOLOGY AND SYPHILOLOGY

## DERMATOLOGY

JOHN B. LUDY, M.D.

**Herpes Zoster**

Ordinary uncomplicated shingles requires little or no treatment and does not interfere with the patient's activities. Some patients, however, run a protracted and stormy course with considerable pain that is difficult to control. Much can be accomplished by skillful topical applications.<sup>1</sup> A simple *calamine lotion with phenol* applied as a constant application to the lesions serves admirably as a soothing wash and as a means of preventing bacterial invasion. Vesicles so treated usually involute at a satisfactory rate and leave no scars. Flexible *colloidion*, with or without antiseptic admixture, employed as a paint or spray prevents secondary infection and serves as a protective coating to lessen local irritation and to curb the reflex arc of pain and hyperesthesia. *Thick cotton pads, dusting powders, and melted paraffin*

are also beneficial. As the vesicles disappear and healthy, noninfected, dry crusts form, these applications being too drying, *boric ointment, lanolin, or vaseline* are preferable. Sometimes it is necessary to prescribe *salicylates, phenacetin, barbiturates, codeine, or morphine* in addition to local measures. An *ethyl chloride spray* over the affected dorsal-root ganglion has been found helpful in reducing pain. *Radiant heat* is comforting.

Many bizarre empirical treatments have been described, and although it is difficult to understand the manner in which they act, it is well to know about them.

*Unfiltered roentgen irradiation* of the skin lesions and *filtered x-ray therapy* to the affected dorsal root ganglions have been found valuable treatments not only in the relief of pain but also in shortening the course of the disease.

**Obstetric pituitrin** may be administered subcutaneously in doses of 0.5 to 1 cc. (8 to 16 minims) daily for three to five days. Pituitrin is contraindicated in the presence of hypertension, coronary disease, myocardial disease, and pregnancy, and it is perhaps better not to use it in elderly people.

**Sodium iodide** in 2-Gm. (30-gr.) doses (10 cc. [160 minims] of a 20 per cent solution) injected intravenously on the first, second, fourth, and seventh days has been reported favorably but care must be taken to avoid iodine allergy and intoxication.

**Diphtheria antitoxin** has been advised (5000 units, repeated in two days, if needed) in the resistant, ophthalmic type of zoster.

**Autohemotherapy** has been in vogue for many years; remove 5 to 10 cc. (80 to 160 minims) of whole blood from the antecubital vein and immediately inject it into the gluteal muscle every day or two.

The pain of herpes zoster responds promptly to injections of a sterile saline solution of **cobra venom**. No depressive, local, or general reactions occur with commercially available material.

Paravertebral injections of 0.5 per cent aqueous **procaine** solution relieves pain for one to two hours and causes regression of the vesicles. Subcutaneous injection of an oil-soluble anesthetic into the hyperalgesic areas gives prompt relief of pain and the anesthesia persists for a week or longer in contrast to the short anesthesia and relief of pain obtained with subcutaneous aqueous novocaine (0.5 to 2 per cent).

Anesthetic oils, such as **Nupercain-Ciba**, **Hollander's formula**, and a modification of it, containing **benzocaine**, **benzyl alcohol**, **phenol**, and **oil of sweet almond**, have been employed. The areas of hyperesthesia were mapped out

by the usual methods, such as pinprick, brush, and pinching, cleansed with alcohol, and infiltrated subcutaneously to the point of total anesthesia. No nerve block was induced. Local reactions included soreness, redness, swelling, and pain at the site of injection. Both immediate and permanent relief is reported for most cases. The clinical course of the skin lesions was not altered; vesicle regression occurred in the expected 7 to 14 days.

**Thiamin chloride** administered subcutaneously in doses of 3000 (about 10 mg.) or more units daily or every second or third day, preferably early in the disease, has been reported favorably by some and as ineffective by others. Both pain and the vesicles have not lasted as long as usual and total disability has been shortened. It is suggested that children, who usually have a mild form of herpes zoster, respond better to thiamin than do older people. The fact that zoster has been reported to occur as an apparent complication of the administration of large doses of vitamin B<sub>1</sub> provides evidence that this vitamin may have an effect on the dorsal root ganglions. In severe and prolonged cases, the oral administration of 3 to 10 mg. of thiamin chloride in association with sedatives, local applications, and autohemotherapy has been followed by striking improvement of both pain and skin lesions. A combination of intradermal and subcutaneous injections of thiamin chloride in the area of the skin eruption daily for three or four days has given striking relief a few hours after the first injection and complete and permanent relief after the third or fourth treatment.

### The Treatment of Lichen Planus by Exposure of the Spine to Large Doses of X-rays

The treatment of lichen planus by irradiating the spinal column with x-rays

was first recorded independently by Pautrier, Hufschmidt, and Gouin in 1924. Pautrier had been impressed by the many signs of nervous abnormality shown by patients with lichen planus, such as nervousness, irritability, the occasional zosteriform distribution of the rash, and the good effects of simple lumbar puncture. He therefore decided to try the method devised by Bordier for the treatment of poliomyelitis, but he did not anticipate the striking success which greeted the use of this treatment in his first case of lichen planus. This encouraged him to try the method more extensively, and his first favorable impressions were confirmed.

Two rather different methods have been used. Pautrier originally exposed the whole spine to a perpendicular dose of 5H (5H = 1sB) through 5 mm. of aluminum; later he modified this, and, using Bordier's technic, exposed eight fields, four on each side of the vertebral column with the tube inclined at 45 degrees, each field receiving 3H through 5 mm. of aluminum. Gouin, on the other hand, merely exposed the interscapular, and in some cases the lumbar, regions to an unfiltered dose of 5H.

The results obtained by both methods were very promising. Pautrier treated 35 cases, all except 3 by "semi-deep, cross-fire" method; in 3 cases, the itching disappeared the same night, and in 4 more it went the following day and in others less quickly; occasionally a second session was necessary. In 13 instances, a complete cure was obtained after one treatment, and in 9 more after two, whereas 8 cases were completely unaffected. Gouin cured 15 cases by a single exposure in the interscapular region and 4 more when an additional dose was given to the lumbar spine; he does not record any failures. Driver cured 10 out of 17 patients, and helped 2 more,

using filtered x-rays in some instances and unfiltered in others.

Several cases have been reported (Hudelo, Hufschmidt) in which x-ray treatment was followed by an exacerbation of the rash, and also of the itching, and this happened in four of Hellier's<sup>2</sup> cases. Pautrier says that he has never seen a case in which any other reaction, such as headache, dizziness, vomiting, or fainting has been observed—noting, in fact, resembling x-ray sickness. In Hellier's series, two patients had nausea and some general upset following their treatment. Generally speaking, the method is more effective in the generalized acute form of lichen planus than in the warty and localized types and that involving the mucous membranes.

The mode of action of x-rays in lichen planus has been discussed at length in the French literature. Pautrier feels that there is a definite action on the nervous system, but that it is impossible as yet to say exactly what part is affected, whether spinal column, nerve roots, or sympathetic system. Gouin, on the other hand, with his unfiltered radiation, considers the site of action must be more superficial; he produces evidence to show that x-rays may influence the sympathetic system in other dermatoses, particularly those in which an upset of the neurovegetative system may be suspected, and finally concludes that the disappearance of the rash in lichen planus is the result of some action of the cutaneous sympathetic system. Neumark and Krynski (1927) think that superficial and deep irradiation both act on the terminal branches of the sympathetic and sensory nerves, producing a reflex action on the spinal cord and sympathetic ganglia. Prieto (1927) suggests that x-rays cause some biological alteration in the skin, capable of influencing the evolution of lichen planus; usually

this causes an amelioration, occasionally an aggravation, and sometimes no effect at all. He therefore treated five cases by exposing an area of 800 sq. cm. on the abdomen in a dose of  $3\frac{1}{2}$ H, apparently unfiltered. In two there was an immediate relief of symptoms, and two more cleared up rapidly after a further exposure to an area on the flanks. In one case there was no improvement by this method, nor by a further treatment using Gouin's technic. He concluded that radiotherapy acts exclusively on the skin, irrespective of the area irradiated, and of any underlying structure. Pautrier dismissed this view, and quoted a case in which irradiation of a leg was not followed by any general improvement.

In an endeavor to evaluate this form of treatment and investigate its mode of action, Hellier treated 60 cases of lichen planus by exposing areas of 160 sq. cm. over the cervical and lumbar spines to 1sB x-rays at 100 kV. through 2 mm. aluminum. Similar-sized areas on the abdomen and chest were exposed in a further 31 patients, and these results have been compared with those in 67 patients treated by intramuscular injections of 0.0325 Gm. (0.5 gr.) of *Enesol*. In a disease such as lichen planus, which may disappear spontaneously, it is difficult to assess results accurately; this is particularly so for those cases treated with *Enesol*, in which 6, 8, or even 12 injections were given at weekly intervals. This has meant that injections were given over a period of three months, and it is probable that some of the cases would have cleared in that time even without treatment; thus the findings are possibly more favorable to *Enesol* than they really should be.

If we compare treatment by *Enesol* with that by x-rays, taking all the cases together, we see that there is a slightly better chance of a cure with *Enesol*—

36 per cent against 29 per cent but that an improvement may be expected in about the same proportion—42 per cent against 41 per cent—or, in other words, some benefit will be derived from *Enesol* in 8 per cent of all cases and from x-rays in 70 per cent. These differences have no statistical significance, and in view of the simplicity of a single dose of x-rays compared with a course of injections, it is suggested that x-rays should be used more frequently.

### Chlorophyll in the Treatment of Ulcers

In 1930, extracts of plant pigment were shown to have stimulating effects on the growth of tissue by Rollet, working under the direction of E. Burgi, of Berne, Switzerland, who has conducted a whole series of investigations on this subject during the past 20 years. Gordonoff and Ludwig in 1935 showed that these extracts have a stimulating effect on growth of tissue cultures *in vitro*. In 1937, in experiments with artificially inflicted wounds on the skin around the spinal column of rabbits and guinea pigs, Burgi was able to show that pure chlorophyll has far greater stimulating power over the regeneration of tissue than has either carotene or xanthophyll. In the United States, Gruskin recently reported encouraging results in some 1200 acute and chronic suppurative conditions treated with chlorophyll.

Among 25 patients with ulcers of various origin, there were 19 who responded favorably to local treatment with *chlorophyll* used in ointment form or in a 0.2 per cent isotonic aqueous solution. Chlorophyll appeared to have a stimulating effect on the supportive tissues.

The chlorophyll used in the study<sup>a</sup> was prepared in two forms, as an ointment and in aqueous solution. The oint-

ment consisted of oil-soluble derivatives of chlorophyll mixed with hydrous wool fat in the proportion of 1 to 28. The aqueous solution was made by dissolving 2 Gm. (30 gr.) of a water-soluble derivative of chlorophyll in a liter of distilled isotonic saline solution.

The ointment was used topically; the solution was used for wet dressings for ulcers which were surrounded by severe inflammatory zones. There were 10 cases of varicose or hypostatic ulcer, 2 cases of acrodermatitis chronica atrophicans, 1 case of a lesion diagnosed as a roentgen ray ulcer, 6 cases of ulcer attributed to trauma or burn, 1 case of a pyogenic ulcer, and 5 cases in which they were unable to find any apparent cause.

Among the 10 varicose or hypostatic ulcers, in 2 cases there was neither granulation tissue nor any other sign of healing, and in 7 there was a rapid filling with granulation tissue. One patient discontinued attendance.

Of the 2 patients whose ulcers were associated with acrodermatitis chronica atrophicans, 1 showed remarkable new granulation tissue; the other discontinued attendance.

The roentgen ray burn healed rapidly in four weeks; it had been treated with various ointments for six months.

All of the six ulcers due to trauma or burn showed rapid granulation and healing, but in one case a sensitivity to chlorophyll developed and treatment was suspended.

The pyogenic ulcer was the result of an abscess of the buttocks which had broken down and did not heal for six weeks. One week after treatment with chlorophyll was instituted, the ulcer shrank to one-fourth its original size.

Of the five patients with ulcers of unknown origin, four showed apparent healing and the fifth discontinued attend-

ance. One of the patients, a woman 60 years of age, had large deep ulcers on both legs. Chlorophyll was used on one leg and the ulcer healed rapidly; on the other leg we used boric acid ointment, and there was no response to the medication.

### Treatment of Psoriasis with Lipotropic Substances Derived from Foodstuffs

The conception of psoriasis as a metabolic disturbance of the skin has received increasing support in recent years.<sup>4</sup>

Substances derived from natural foodstuffs have been found to have a therapeutic effect on the eruption of psoriasis. Both *soybean lecithin* and *defatted wheat germ* contain *inositol*. The cephalin fraction of the soybean contains from 5 to 10 per cent crude inositol and the defatted wheat germ about 0.25 per cent. It seems doubtful that the therapeutic effect is due to inositol alone. The lecithin fraction of the soybean product is also a rich source of *choline* (about 3 per cent), while the defatted wheat germ is poor in this substance. In contradistinction, the wheat germ is a well balanced vitamin B complex, containing biotin and also iron, manganese, and other minerals, while these substances are lacking in the soybean phosphatides.

The question of which component or components are responsible for the lipotropic and antipsoriatic effect of soybean phosphatides and defatted wheat germ therefore cannot be answered at present. It remains to be seen whether there is a complementary action between these substances or whether there are patients who respond better to the soybean phosphatides than to defatted wheat germ and *vice versa*.

The average daily dose of the soybean lecithin varied between 30 and 60 Gm.



(8 to 16 drachms). With the disappearance of the lesions, the patients were kept on a maintenance dose of 4 to 8 Gm. (60 to 120 gr.) daily. The defatted wheat germ was given in doses of 30 to 45 Gm. (8 to 12 drachms) a day, and the maintenance dose was 15 to 30 Gm. (4 to 8 drachms) daily. Local therapy, particularly a *mild tar cream*, seemed to hasten the involution of the lesions. An attempt to improve simultaneously the constitutional anomalies by removal of focal infection, by rest, by psychotherapy, and by nonspecific therapy and intelligent endocrine treatment may further reduce the percentage of failures. The experience of Dragstedt and his coworkers with *lipocaic* suggests that there will remain a group of cases of psoriasis that will present further therapeutic problems.

About 40 patients with chronic psoriasis were under treatment with either the wheat germ or the soybean lecithin and with or without the addition of local therapy. In most instances, within a few weeks of administration of these lipotropic substances new psoriatic patches ceased to appear and a gradual involution of the plaques began. Three patients, each with an initial attack of psoriasis of less than six weeks' duration, had complete clearing in less than a month. The only therapy was administration of soybean lecithin and local application of 3 per cent colloidal tar ointment. In some cases of chronic psoriasis the condition has proved resistant to this type of therapy.

### Use of Urea in Hand Creams

The use of *urea* (carbamide) has been applied to a wide variety of medical conditions in the past ten years. It has been employed most frequently in the treatment of infections, particularly infected wounds and ulcers, infections of the ears,

infected tooth sockets and infected malignant growths, and of burns. It has been recommended also for the treatment of scar tissue, for the eradication of warts, and even as a preventive against dental caries.

Synthetic urea is readily available, it is stable, soluble in water, and easily incorporated into solutions, lotions, ointment bases, and dusting powders.<sup>5</sup> It apparently is nontoxic when absorbed and nonirritating when applied to wounds, and it has the added advantage of being inexpensive. It would seem, therefore, to be a suitable ingredient for a hand cream, for it incorporates into a special kind of cosmetic a drug that, while useful, is free from danger on absorption.

The urea was used in a concentration of 3 per cent, the vehicle being a vanishing cream base consisting of "fatty materials" (soluble stearate soaps and liquid petrolatum) dispersed in a relatively large amount of water (70 per cent). The remaining components included glycerin, tragacanth, and perfume.

Patch tests with the cream were performed on 500 persons, 400 of whom were women ranging in age from 14 to 84 years. The majority were between 20 and 40 years of age, an age group likely to comprise those most likely to use hand creams. They were all patients confined to the hospital for various diseases, 66 of them for cutaneous diseases, some for diseases of an allergic nature, and others for infections, fractures, metabolic disturbances, etc.—patients of the usual large general hospital population. They included persons with dark skins and fair skins, thick skins and thin skins, the old and the young—in all, a fair cross section of likely consumers of hand creams. The patch test study covered a period of three months, January, February, and March, the time selected allowing to some extent for any barometric



influences that might play a rôle in the production of reactions. The sites selected for the tests were various areas where the skin is thin—the V of the neck, the arm, the abdomen, the wrists, and the hands. The tests were performed in the conventional manner with a one-inch square of gauze containing the cream, which was covered by a larger square of thin waxed paper, and this in turn was strapped to the skin with adhesive tape for 48 hours. The sites were then examined and the majority were re-examined at 2-day intervals for 2 weeks. Not a single positive reaction was noted in the 500 subjects, albeit there might have been expected a few such responses to the vanishing cream vehicle, which was scented. The results seem to indicate that the cream containing urea in 3 per cent concentration did not constitute a primary irritant or have a high irritant index.

Of 66 patients with various types of eczematous eruptions for whom the urea cream was prescribed, 40 presented patches of slight dermatitis comparable to chapped skin. The application of urea cream three times daily effected a rather rapid improvement of such dermatitis. However, in cases of acute erythematopapular eruptions and of subacute eruptions, the dermatitis was made worse. The irritation was apparently due to the cream base, for in these cases urea in 3 per cent concentration in a nonscented cold cream base was well tolerated.

**Comment**—The story of the use of urea in medicine is not without interest. Folklore is rich in references to the healing properties of urine. The Babylonians of about 800 B. C. are known to have used it, and even today it is favored as a healing agent by peasantry in various parts of the world. The use of a waste product, however, for therapeutic purposes was doomed never to gain wide

favor; to urea, too, because it was first isolated from urine, has been attached a stigma difficult to overcome. Despite its extensive, empiric use in urine, not until recent years was urea developed as a therapeutic agent on a sound basis. In 1935, Robinson, in the course of investigating the curative action of surgical maggots in infected lesions, found that *allantoin*, an excretion of the maggot, functioned as the healing agent. Allantoin on hydrolysis yields urea, and Robinson then demonstrated it was the urea that was responsible for the healing action attributed to the maggot and to allantoin.

Although the first recorded medical use of urea as such was in 1829, it was not until 1915 that Symmers and Kirk reported on an extensive experience with its use in many varieties of wounds and infections, with uniformly good results. Other investigators subsequently reported equally good results in a large number of cases, results that prompted Robinson to predict that allantoin, then in high favor, would soon be replaced in popularity by its "extraordinary chemical associate, urea." Urea then did attract considerable attention in medicine, until the development of the sulfonamide compounds for the treatment of infections again made the fate of urea uncertain. Recently, however, excellent results have been reported from the use of urea in combination with *sulfanilamide* for infected wounds and as a prophylactic treatment with amputations and other surgical procedures. The efficacy of each drug apparently was enhanced by the combination. In fact, since this report, it had been the author's practice to treat all pyodermas with a mixture of urea and *sulfathiazole*, 5 per cent of each, in an emulsifying base, with, he believes, superior results.

For medical use there is a pure synthetic form of urea, which is odorless, stable, white, crystalline, and solid, with a rather cool, flat taste. It may be applied directly to a wound in the form of crystals, or, being readily soluble, it may be applied in dilute or concentrated aqueous solution, as an ointment prepared with a nongreasy base, such as a vanishing cream, or in surgical jelly. Urea may also be incorporated in a dusting powder. In the treatment of wounds it is recommended that urea be kept in direct contact, for it is rapidly absorbed and has no residual action. A high concentration of urea, when applied to open wounds, produces temporary pain because of its hypertonic action. When dilute it causes no discomfort, and there is a wide latitude in the concentration which can be used effectively. If used in ointment form, it is best incorporated in a firm, greaseless base, for urea tends to soften the vehicle. Its main action in low dilutions seems to be as a stimulus to proliferation of the cells of granulation tissue, with increased development of capillaries.

### Pediculosis Capitis

**Treatment**—The older methods for the control of head lice can be found in various textbooks. Objections to these treatments arise almost as they are described. *Shaving the scalp* is effective but hardly appealing. Soaking the hair for an hour in 70 per cent *alcohol*, 2 per cent *phenol*, *veratrine*, *larkspur*, *vinegar*, or similar preparations is time-consuming and only too often ineffective or irritant. *Essential oils* are effective in adequate dosage but expensive and odorous. *Kerosene*, *crude petroleum*, and *xylene* similarly are liable to leave an odor unless washed out thoroughly and are unpleasant. The fumigation of the scalp by *sulfur dioxide*, mentioned by

Buxton as a common practice in Germany, is clumsy and leaves the head immediately susceptible to reinfection. The removal of head lice by a fine-toothed comb is tedious, to say the least. Probably the best of the older methods is the inunction of the scalp with ointment containing such agents as *xylene*, *pyrethrum*, or *rotenone*. More recently Busvine and Buxton have incorporated *thiocyanates in ointments* and report excellent results. Yet such grease may be unpleasant or tedious to rub into women's hair. The ideal method for treating pediculosis capitis should be by a lotion, since only a liquid can easily penetrate the entire hair and leave a residual for prolonged action. The fluid should rapidly kill lice and nits, should not have unpleasant properties, such as greasiness, staining, or odor, and should be both cheap and lasting. Systematic laboratory studies revealed several materials with these properties.<sup>6</sup> *Phenyl cellosolve* and *benzyl cellosolve* (Cellosolve is the trade name for certain solvents made by the Carbon and Carbide Chemicals Corporation) were the most efficient and were readily available. Preliminary trials indicated that, if a 10 per cent concentration of these cellosolves was put onto cloth, it killed all lice on the cloth in less than three hours; nits exposed to the same dosage failed to hatch. A 40 per cent concentration of phenyl cellosolve placed on the head was not irritant and could be detected for about four days. Therefore clinical trials of these agents were made. For simplicity only phenyl cellosolve was used on human beings. The formula used was phenyl cellosolve, 40 per cent; ethanol, 30 per cent; water, 25 per cent, and methyl salicylate, 5 per cent. The nurses were asked to apply the lotion to the head so that the hair was thoroughly wet and cautioned to keep the fluid out of the eyes and mouths

of the children. No further treatment was used. The results were quite satisfactory. No live lice were ever found after a single treatment. No irritation was observed except a brief mild tingling if the lotion was rubbed into the scalp.

The chief advantages of the lotion described were ease of application, rapidity of action, freedom from irritant action, and efficiency against both insects and eggs. No suggestion is made that the lotion described constitutes the only effective treatment of pediculosis capitis, but it is emphasized that the usual methods for killing pediculi are clumsy and relatively ineffective, and the type of lotion described should be generally adopted for the eradication of head lice.

### Chigger Bites

Chiggers are found, during the warmer months, all over the world, in the tropical and temperate zones, on mountains and in valleys, but especially near lakes and rivers.

The chigger is a larva, or immature organism, with six legs; the adult has eight legs, like all spiders, and is harmless.

When a person passes through a chigger-infested area, they invade the skin and run at the rate of about 10 cm. (4 inches) per minute, until they meet some obstruction, such as a garter, belt, or other constriction in the clothing (although some are scattered elsewhere). They usually attach themselves within a few hours.

One or more mites may be anchored at the orifice of a single follicle. They are too large to enter the follicle completely. They do not burrow in the skin, but merely pierce the outer horny layer of the epidermis with their sharp foreclaws. An irritating salivary secretion flows from the mouth between the foreclaws into the tiny wound in the host's

epidermis. This secretion dissolves the epidermal cells, and the resulting fluid is then sucked up by the chigger as food. After a few hours the chigger is engorged and drops off, no longer a parasite, to continue its development into the mature eight-legged form.

As a rule, one chigger inflicts one bite, and only one. The resulting papule varies from the size of a large pinhead to that of a bean or small coin, and it may be surmounted by a small pinhead-size blister. It lasts for a week or two. The itching is more or less intense, and usually worse on the second or third day; and, of course, scratching may change the picture completely and lead to secondary infection or to the development of hives. More chiggers may remain in the clothing and thus invade the skin later to produce new lesions.

**Diagnosis**—As a rule there is not much difficulty in diagnosis.<sup>7</sup> The bites of spiders or of flying insects, including mosquitoes, bees, wasps, black flies, sand flies, gnats, and midges, often bear some resemblance to the earlier stages of the chigger bite, but usually they are single, or at any rate less numerous than chigger bites, are located on exposed parts rather than on covered areas, are usually felt immediately and are seldom hemorrhagic. The bite of the common flea or that of the sand flea may also resemble the first stage of the lesion caused by chiggers. The sand flea usually attacks the feet and ankles, and some persons may be bitten by cat fleas and rat fleas in the same manner. Bedbug bites may sometimes cause confusion in diagnosis, but their central punctum and short duration facilitate differentiation. The possibility of confusion with lesions due to the brown-tailed moth, tick bites, and infestation with poultry itch must also be considered at times.

**Treatment**—In the treatment for chigger bites, there are three objectives: (1) The destruction or removal of all remaining parasites, both free and attached; (2) the relief of the severe itching by palliative measures; (3) the treatment or prevention of secondary infection. The mites, if any remain, are most readily removed by an application of *benzine*, *kerosene*, or *copper compound*, followed by *bathing* for a half hour with plenty of soap lather. This should be followed by thorough rinsing with fresh water and patting dry rather than rubbing with a towel. Since active mites may remain in infested clothing, it is advisable that all articles be boiled or sent to a dry cleaner.

Since the objective and subjective symptoms usually continue unabated for days after the parasite has been removed, the fulfillment of the second and third objectives is of the greatest importance. A variety of palliative measures has been suggested. Brief applications of *rubbing alcohol* (70 per cent) to the affected areas, followed immediately by a mild antiseptic antipruritic ointment, is satisfactory. A clean and generally effective application is *boric acid ointment*, *U.S.P.*, to which may be added 1 to 2 per cent of *phenol*, the strength, of course, being in inverse proportion to the area of skin to be covered, and 0.2 per cent of *menthol*. This ointment should be applied sparingly at least three times a day and also used as needed to relieve itching; it is to be rubbed in gently, and the remainder is wiped off with cotton. A little plain talc may then be dusted over the surface. These applications are made after the daily bath and at least two other times daily. Scratching must be prevented, and canvas gloves may have to be worn during sleep for this purpose. These measures fulfill both the second and third objectives as a rule.

But, if serious secondary infection has occurred, of course other measures may be used as indicated.

**Prevention** *Sulfur* has long been recommended as a repellent. One investigator dusted it uniformly over the skin or into the clothing with a shaker, and found it effective. It should be dusted freely on the legs and ankles and inside the hose and trousers. As an added precaution, one should bathe as promptly as possible after exposure to chiggers in order to remove the somewhat irritating sulfur and to destroy any surviving mites. This is an effective scheme of protection; but, of course, the best method is the elimination of local foci of chiggers. It must be remembered that chiggers may occur not only in thickets and fields, but also about golf courses and in our own gardens and vacant lots. They usually disappear if weeds and underbrush are cleared away and the grass is kept short by frequent mowing, especially if the vegetation is thoroughly sprayed with sulfur by means of a dust gun or dust blower. It is recommended that 50 pounds of sulfur per acre be used. Infested lawns have been freed from chiggers by the dragging over them of a piece of canvas or sacking saturated with kerosene; but it should not be allowed to drip or remain long in one place or the grass may be killed.

### Pruritus and Kraurosis Vulvae

**Treatment**—The hormonal treatment of essential pruritus, kraurosis, and leukoplakia of the vulva gives a more favorable prospect for alleviating the symptoms and curing the conditions than any known form of therapy.<sup>8</sup> Of 54 cases of pruritus, 74 per cent responded to such treatment and 8 of 14 patients with primary kraurosis and leukoplakic vulvitis were similarly benefited.

The following treatment scheme is used: During the first 1 to 3 weeks, local treatment only was given. This consisted of vulval inunction with a salve, each dose representing the equivalent of 2000 and 5000 I.U. of *estrone*, depending on the severity of the condition, the lower or higher concentration was used. The ointment was administered twice a day. The skin was thoroughly cleansed prior to treatment. A cotton pad soaked with warm water was applied to the area for five minutes in order to facilitate absorption. The ointment was rubbed gently into the affected area until it disappeared. In the second, third, or fourth week, particularly in those instances exhibiting hypoövarianism aside from the vulval changes, parenteral therapy was instituted consisting of two injections of 10,000 R.U. of *estradiol benzoate* per week. The ointment was applied morning and night on days when injections were not given. Eight weeks after the initiation of local therapy, the parenteral dosage was decreased to 10,000 R.U. a week, the topical medication being continued at the same dosage. The whole course of therapy required 12 weeks. By decreasing the dosage of the parenterally administered hormone, as compared with the previous scheme, side effects of vaginal bleeding and discharge were mostly eliminated in the present series. However, parenteral hormone administration was not completely discontinued because it favorably influences the general condition of the patient and the systemic manifestations of the menopause.

The majority of cases of essential pruritus vulvae, kraurosis vulvae, and leukoplakic vulvitis occur after the menopause. In view of the fact that a high percentage of cures in such cases is effected by estrogenic therapy, it is apparent that declining ovarian activity is an impor-

tant etiologic factor. However, there are other causative factors in the pathogenesis of these disorders, such as predisposition of the vulval tissues, familial factors, and probably other factors unknown to us. That constitutional factors play a rôle is manifested by the fact that only a small fraction of menopausal women suffer from pruritus or kraurosis vulvae; furthermore, such disorders are found in women of the reproductive age group, even in girls shortly after puberty. Among the familial factors in cases of essential pruritus vulvae were found disposition toward functional ovarian disturbances, myomata, obesity, metabolic disorders, and diabetes, as well as functional disturbances of other glands.

It is significant that of the cases of kraurosis and leukoplakia which were refractory to hormone treatment, the majority belonged to the group of young women with apparently normal ovarian function. Failure of therapy in all likelihood indicates that in these instances elements other than decreased ovarian activity were etiologic factors in the disorders. The importance of vitamin A deficiency has been stressed. Also it is noteworthy that over 13 per cent of the patients with kraurosis and leukoplakia, the etiology of which still remains obscure, had a previous syphilitic infection.

**A New Treatment for Intractable Pruritus Vulvae**—Intractable pruritus vulvae has been a distressing and annoying disorder both to patient and to doctor. We see all types of pruritus vulvae but the intractable type offers a real challenge to the clinician as to therapy and its effects.

A series of 15 cases was begun in June, 1942.<sup>9</sup> The procedure is simple and practical, requiring no intricate apparatus, medicines, or assistance. The patient is not incapacitated and it carries no risks or any complications. The solution

used for injection consists basically of an anesthetic (*procaine*, 2 per cent), *benzyl alcohol*, 5 per cent, and a vehicle which may be olive oil, peanut, or almond oil.

The pubic and vulvar hair is not shaved. The vulva is cleansed with green soap and flushed with water. The injection is made in four directions, along the length of the labia majora and minora on both sides, across and above the anal region. One-fourth inch away from the usual inflamed border laterally, the needle (21 gauge, 2 inch, or spinal) is introduced at the upper pole of the labia and is carried down to the lower pole before injection is actually begun. When the point of the needle is felt at the lower angle, then the oil is injected and the needle gradually withdrawn upward until the upper pole of the labia is reached. The injection is made fairly deep in the fatty parts of the labia. Five cc. (80 minims) are used for each labium laterally; 2.5 cc. (40 minims) for the upper and lower injections. Occasionally, a vein is punctured but this has no serious complications.

Subjective symptoms are markedly diminished or completely abated in from three to seven days.

The vulva will present a slight tumefaction of a fibrous consistency for a week but a smaller fibrotic cordlike structure remains from two to four weeks. The authors have seen no sloughing in any of their cases. Occasionally, a severe case may require a second injection. Only one-half of the original amount is used and not sooner than two to three weeks after the first injection. The authors recommend warm baths and washing the vulvar parts with soap and water after the injections are given. This will aid in eliminating the secondary infection which is so often present prior to the treatment.

### Skin Disturbances in Diabetes Mellitus

Skin disturbances are common in diabetes mellitus. Furuncles, carbuncles, and other pyogenous as well as mycotic infections may occur alone or combined as a result of this vulnerability. Pellagrous dermatitis in diabetes is especially frequent and is often diagnosed and treated as psoriasis vulgaris. Pruritus vulvae and ani in diabetes are a manifestation in pellagra.

#### Relation to Vitamin Deficiencies

A careful history and physical examination in these cases will invariably disclose manifestations of a multiple vitamin deficiency, a beefy or smooth tongue, cheilosis and gastrointestinal, genitourinary, neurological, mental, and other disturbances. These signs may precede or follow the skin disturbances.<sup>10</sup>

There are several causes and numerous predisposing factors for the development of deficiency states in diabetes mellitus. The diet is not infrequently deficient in the components of vitamin B complex. Many diabetic patients have no teeth or have poor artificial dentures, and, as a result, the food is poorly masticated. Some have idiosyncrasies to various foods. Liver function may be impaired as can be suspected from enlargement of the liver, and may interfere with the storage of the metabolism of the vitamins; moreover, the enlargement of the liver itself may be the result of a vitamin deficiency. Loss of weight, infections, gastrointestinal disturbances, acidosis, overindulgence in alcohol, and operations may act as precipitating factors in the development of the deficiency symptoms in diabetes mellitus.

The skin lesions may improve, remain unchanged, or even become aggravated with the control of the diabetes by diet with or without insulin. They always respond to treatment with nicotinic acid.



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## SYPHILOLOGY

CARROLL SPAULDING WRIGHT, B.S., M. D.

It is possible that the year 1943 will stand out in the annals of medicine as the year in which *penicillin* was discovered to be an easy and complete cure for syphilis. The medical literature dealing with syphilis for the year 1943 emphasized new and intensive methods of treating this disease, but in September the announcement of John E. Mahoney, R. C. Arnold, and A. Harris at the meeting of the American Health Association in New York, that penicillin might prove the weapon eventually to conquer both syphilis and gonorrhea startled the medical world. The report included only four cases of syphilis, but these were exceptionally well controlled and were believed to be cured. Each of the four patients received 25,000 Oxford units of the drug intramuscularly every four hours for eight days or a total of 1,200,000 units. Dark-field examination was negative about seven hours after treatment was started and patients became gradually seronegative. One hundred days after treatment was discontinued, no trace of the disease could be detected in the patients' blood by any known serological test. Penicillin seems to be absolutely safe. If later studies reveal penicillin to be a cure for syphilis, an entirely new chapter on therapy must be written and the hope of largely eradicating the disease may be attained.

### Intensive Methods of Treating Syphilis

Evidence as presented by Cole, Heisel, and Stroud<sup>1</sup> show that early syphilis is being cured by intensive treatment methods, whether it be intravenous drip, the syringe technic, multiple injections of Eagle, or fever therapy and intravenous drip or syringe treatment plus fever. The patients are not only cured but, as Schoch and Alexander<sup>2</sup> point out, they are even being reinfected in agreeable numbers.

Stokes<sup>3</sup> has recently reviewed the difficult problem. He points out that a new system of treatment of syphilis must equal or surpass the curative expectancy of the older ones, lead to less infectious relapses, cure more mothers and protect more children, and lessen the incidence of cardiovascular and central nervous system syphilis. On the other hand, when the relatively benign character of much early syphilis is considered, 40 to 50 per cent of cases curing themselves, and the fact that with relatively small amounts of treatment, if the defense mechanism is not disturbed, this may even be raised to as high as 70 per cent, here the public health problem of syphilis is being completely ignored, especially in wartime. He quite properly insists that evaluation of a system of treatment requires two to four years as

far as relapse is concerned and ten years for evidence of progression. A new system must be cheap and rapid, control the lapse problem, and allow treatment of more persons per unit of time, personnel, and equipment. All these arguments are, of course, in favor of intensive methods, though, as Stokes notes, the man cured with intravenous drip or with fever plus the chemotherapy must be followed afterward even as much as his lady friend treated by the longer but safer 18 months method. And, too, he states that with intensive methods, wherein patients are even paid for follow-up visits, the loss rate is 17 per cent; in some clinics, 6 to 20 per cent up to six months. He thinks that long term treatment in the modern syphilis clinic is carried through in 25 per cent of the early cases and 50 per cent ultimately receive satisfactory irregular treatment. Moreover, that in really good clinics with effective case holdings, it may be raised to 50 per cent with 70 to 80 per cent ultimately receiving satisfactory irregular treatment. In this connection, one should remember that not just half a dozen clinics are being dealt with, but the run-of-mine clinic throughout the United States. How well is this clinic holding its cases? It is not necessary to answer: the record is *bad*. He is probably right in his contention that the percentage of relapse is about the same with intensive methods as with conventional treatment. Cole<sup>1</sup> and his cowriters agree that for the present, at least, intensive therapy should be reserved for relatively acute syphilis—not later than early latent.

Stokes<sup>2</sup> says that for 4871 patients treated with all the intensive methods, there was a mortality of 1:220 and a morbidity of nonfatal encephalitis of 1:160. Shaffer<sup>4</sup> makes the figure for mortality 0.3 per cent. It is true that

with older methods encephalopathy is very rare; he puts it 1:20,000. He also adds that deaths from mapharsen are thus far only six after administration of millions of doses. He thinks that the death rate is probably 100 to 200 times that from older methods. To this must be added the ultimate mortality or morbidity of an enormous number of early uncoöperative syphilitic patients who take a few treatments and lapse. And, too, how many new infections do they pass on and thus keep the syphilitic ball rolling? How many mothers and how many babies are infected by them before their disease gets so old that it is no longer transmissible. Moreover, would not such an intensive technic be a partial answer to the expert help problem in the clinics? The patient receives his treatment and then is through except for follow-up and occasional examinations.

Vonderlehr and Usilton<sup>3</sup> have recently analyzed the 1,895,778 serologic reports of men aged 21 to 35 who were examined under the Selective Service Act of 1940. The rate of prevalence of syphilis among the entire male population between 21 and 35 is estimated to be 47.7 per 1000. However, the rate of prevalence among Negro selectees is 253.3 per 1000 and among white selectees 17.4 per 1000. Moreover, if one turns to urban centers in the South it is found that the rate of prevalence among Negro men ran 413 per 1000 in Florida, 407 in Georgia, 358 in Arkansas, 339 in Maryland, 431 in Mississippi, 384 in Texas, 417 in South Carolina, and so on. Unfortunately, these data present the crux of the whole syphilis problem. The rate of prevalence is highest among the most ignorant and least coöperative part of the population. The common complaint from all workers in syphilotherapy is difficulty in holding the uncoöperative patient. A few treatments and he is gone.



With those forms of treatment in which the patient is hospitalized and receives his full complement, Cole, Heisel, and Stroud<sup>1</sup> are at least sure that he or she has this under his or her skin. True, a certain number will relapse, but this is a small number compared to the number lost under any routine form of treatment. Moreover, the public health problems, especially regarding syphilis, are paramount in the midst of a world war. It is their opinion that at least for the duration all such uncoöperative patients with early syphilis as come to public health clinics should be hospitalized and treated by intensive methods, *i. e.*, the *intravenous drip*, the *Schoch method*, the *hypertherm treatment* plus intravenous medication, or by the *Thomas and Wexler method*. Stokes thinks the future should look to the multiple dose technic of Eagle and Hogan or to a combination of two or three sharp prolonged pyrexial rises with massive dose *mapharsen therapy* by drip or multiple injections. For such patients as are seen in clinics the answer is not to be found in the Eagle technic—the patient must be hospitalized and treated while hospitalized and for that reason the Thomas and Wexler technic with daily injections of *mapharsen*, 0.060 Gm. (1 grain), plus *intravenous typhoid-paratyphoid* on the second, fourth, sixth, and eighth days, the five-day intravenous drip perhaps with added *soluble bismuth* intramuscularly, or the *hypertherm plus intravenous chemotherapy* are preferable. It stands to reason that such therapy should be administered only by experts in the field, trained to meet any emergency. Attempts at this type of therapy by the tyro can lead only to disaster. Moreover, such therapy requires a competent house staff and nursing staff skilled in handling such cases. The next few years are going to do much

in answering this great problem—the intensive therapy of syphilis. And, apparently, American medicine is at the fore in handling this grave question.

### The Five Day Treatment of Early Syphilis

The undeniable advantages of the five-day treatment of early syphilis as pointed out by Rattner<sup>6</sup> are that (1) it apparently cures a majority of patients, (2) it affords rapid control of infectiousness, (3) it gives no opportunity for lapse in treatment, and (4) there is a considerable saving to the patient in both time and expense.

An effective "speed-up" method of treatment is desirable at this time, for it may be anticipated from statistics of past wars and the experience of England in the last year that there will be a sharp increase in syphilis. The question of the safety of the method has been the greatest drawback to its general adoption, for the incidence of cerebral reactions, some fatal, far exceeds the recorded incidence of similar reactions from standard treatment. Proponents of the five-day method suggest, however, that the reports of fatalities from conventional treatment are not a true reflection of their actual incidence, and furthermore that the risk involved with the rapid method is far outweighed by the serious late complications of syphilis which result from inadequate standard treatment.

**Technic**—Before treatment, the physical status of each patient should be determined with the help of laboratory studies which included blood serologic tests, particularly the Kahn quantitative test, a complete blood count, urinalysis including tests for urobilinogen, icterus index, blood chemical determinations, and a roentgenogram of the heart. The test for urobilinogen has been found to be a most valuable procedure as an

indication of the "course of events," and it became a rigid rule never to begin treatment until the morning specimen of urine had been tested for the presence of urobilinogen.

The daily dose of arsenic, regardless of age, weight, or sex of the patient, recommended by Rattner, is 0.24 Gm. (4 gr.) of *mapharsen* dissolved in 2000 cc. of 5 per cent dextrose solution. The supply for the entire day is made up in the morning and, with the solution maintained at room temperature, it is administered intravenously by the drip method for a period of about eight hours. A vein on the dorsum of the hand or one on the outer surface of the forearm near the wrist is selected in order to permit free motion of the elbow. The arms are alternated each day. The needles employed are the number 20 deep injection type, 1½ inches long. They are inserted up to the hub and then transfixed to the skin with adhesive tape. In addition, soluble *bismuth sodium tartrate* is injected intramuscularly into the buttocks in an amount equivalent to 22 mg. of bismuth each day for the five days.

The patients require no special preparations before treatment. On the first day solid food is withheld to alleviate nausea, but thereafter the patients receive the ordinary ward diet. After completion of the day's treatment they are permitted to be up and about.

On the sixth day the blood is again examined serologically and also the spinal fluid. The patients are discharged from the hospital the following day and instructed to return at monthly intervals for examination, particularly for serologic studies by the quantitative method. The clinical application of the quantitative test is a relatively recent advance which has proved invaluable as a therapeutic index, for only by frequent observations of the progressive rise or fall

of the serum titer of a patient's blood can one make an intelligent appraisal of his serologic status—whether serofast, improving, or relapsing. Rattner summarizes his results as follows:

"1. The five-day treatment method was studied in 481 cases of syphilis. Of this number 421 completed the full course of five-day treatment, 310 of them with mapharsen alone and 111 with a combination of mapharsen and bismuth used concurrently.

"2. There were no fatalities in the group, but there were three instances of serious cerebral reactions and a high incidence of unimportant minor reactions. Treatment was discontinued in 6 per cent of the cases because of the development of complicating symptoms. Three per cent of the candidates were rejected as unsuited for the treatment because of physical defects.

"3. The study emphasized the value of reliably performed quantitative serologic tests as a therapeutic index and focused attention on the questions of reinfection and superinfection. In the group studied there were at least 15 instances of reinfection.

"4. The period of observation is too short to permit final conclusions, but the results to date indicate that the use of mapharsen alone produced satisfactory results from one course of treatment in 86 per cent of the cases, one course of the arsenic-bismuth combination produced satisfactory results in approximately 95 per cent of the cases, and a second course of treatment, administered usually six months after the first course, apparently 'cured' practically all of those who failed the first time."

### Reinfection as a Measure of the Curability of Early Syphilis

Most students of the disease syphilis, whether in experimental or clinical fields,

believe that reinfection under certain circumstances occurs, although as Moore<sup>7</sup> points out there are wide differences of opinion as to the criteria which permit such a diagnosis in man. Stokes and collaborators in 1931 described 17 requirements for "indisputable" reinfection, whereas Moore is satisfied with three relatively simple points, as follows:

1. There must be proof that the patient had syphilis prior to the occurrence of the supposed second infection, and this proof must rest on the demonstration of spirochetes in a lesion or the occurrence of a verified positive STS (serologic test for syphilis) in the blood serum, or both, and not on clinical judgment alone.

2. After an interval following anti-syphilitic treatment and at a site other than that of the primary lesion of the first infection, there must develop a lesion with the clinical characteristics of a chancre, in which spirochetes can be demonstrated.

3. At the time of the supposed second infection, the STS must be negative; and while under observation and during a period when treatment is purposely withheld, the STS becomes positive or the patient develops outspoken secondary syphilis.

According to Moore, it is generally agreed that reinfection, whether in experimental animals or in man, occurs only (or almost only) in those cases in which treatment is begun during the early weeks or months of infection. There is experimental evidence to indicate that reinfection may occur in the presence of persistent infection (*i. e.*, superinfection), or that it may fail to occur because of persistent immunity, even though the first infection has been abolished. Nevertheless, and in spite of all the experimental and clinical pitfalls, most clinicians tend, and probably cor-

rectly, to regard reinfection in man as evidence of cure of the first infection.

Whatever criteria of definition of reinfection in man are employed, the phenomenon is a rare one in patients treated by standard methods (continuous treatment with *alternating arsenical* and *heavy metal* for 12 to 18 months). How rare is exemplified by the data of Halley and Wassermann, who in 1928 found that only 229 of 676 reported cases in the literature satisfied the first two of the three simple requirements outlined above; and by the C. C. G. observation that only 31 of more than 6000 patients with early syphilis were subsequently observed with probable (not indisputable) second infection. Utilizing these and other data, it may be estimated that the chance of observed reinfection in a patient with early syphilis treated by standard routine methods is roughly one in 200.

In the minds of most observers, these long odds have been explained on the basis of one or both of two assumptions: that the burnt child shuns the fire, or that the supposed biologic "cure" of the first infection has been accompanied by persistent immunity against reinfection. Obviously, neither of these assumptions may be justified.

Schoch and Alexander<sup>2</sup> point out that in patients with early syphilis treated with intensive arsenotherapy, reinfection may be a relatively frequent phenomenon. Up to this point, the published reports of workers with intensive treatment methods, recognizing the extreme difficulty of differentiating reinfection from infectious relapse, have leaned to the side of conservatism, and have classified all such cases as relapse, and therefore as treatment failures. However, the clinical evidence in favor of reinfection in many such patients is at least as strong as in the heretofore accepted ex-

amples of reinfection in patients treated by standard methods.

It seems entirely probable, on the basis of currently available information (much of it unpublished) concerning patients treated with one or another type of intensive therapy, that reinfection, acceptable as such by the three simple criteria above, has occurred in at least 6 per cent of the patients so treated. Moreover, most of these supposed reinfections have been observed within the first year after treatment. In view of the short periods of post-treatment observation so far available in intensively treated patients, more such reinfections may still be expected to occur.

Whether these cases, observed after any form of treatment, represent reinfection, superinfection, or relapse, is a point which cannot be settled with existing knowledge; but the argument is academic and beside the point that the introduction of intensive arsenotherapy has apparently, perhaps as much as twelve-fold, increased their incidence. This fact requires explanation.

### Treatment of Syphilis with Clorarsen

New drugs, which give promise of being of therapeutic value, are always welcome, particularly in the treatment of such a disease as syphilis. Kampmeier and Henning<sup>8</sup> gave 4348 injections of *clorarsen* (3 amino-4-hydroxy-phenyldichlorarsine hydrochloride) to 251 syphilitics, the majority of whom were in the early stages of the disease. The efficacy of this drug was determined by (1) the rapidity of producing darkfield negativity, (2) the healing of lesions, (3) the reversal of serologic tests, and (4) a low frequency of spinal fluid abnormalities.

The scheme of treatment consisted of 8 to 10 injections of *arsenic* in the first course, accompanied by *bismuth* at the first 3 injections which are given at

about 4-day intervals. Subsequent treatment was continuous, consisting of alternate courses of weekly injections of bismuth and arsenic. In this study the first 75 cases of acute syphilis received clorarsen *only* during the first course, so that the evaluation of darkfield examinations and the healing of lesions was uncomplicated by bismuth. Clorarsen was given in 8 or 10 injections for the first course. The dosage used was 0.045 and 0.067 Gm. ( $\frac{3}{4}$  and 1 gr.) for patients who would have received 0.45 and 0.6 Gm. ( $\frac{3}{4}$  and 1 gr.) of *neoarsphenamine*, respectively, on the basis of weight and sex.

A single therapeutic dose produced darkfield negativity within 24 hours in 42 or 45 cases of infectious syphilis studied.

Healing of acute lesions was prompt. In cases having complete records, all chancres were healed completely by the end of the fourth week; all secondary and secondary relapse lesions were healed by the end of the fifth week. Over 50 per cent of the primary and secondary lesions were healed by the end of the second week.

A statistical study of the chance of reversal of the blood Wassermann and Kahn tests under continuous antisymphilitic treatment with clorarsen and bismuth was made. The chance of reversal of the Wassermann test in primary syphilis was 100 per cent by the seventeenth to the twentieth week, and in secondary syphilis it was 91 per cent by the twenty-first to the twenty-fourth week. The probability of reversal of the Kahn test in acute syphilis was delayed over that of the Wassermann test. Seroreversal in early latency is definitely later than in acute syphilis.

Spinal fluid examination was done in 38 cases of early syphilis. Fifteen had spinal fluid examinations after the sec-

ond course of clorarsen. Only one of these had an abnormal spinal fluid which later became negative. Thus 37 had negative spinal fluids after two or more courses of clorarsen.

No serious untoward reactions were encountered. Nausea, vomiting, and diarrhea were the most common reactions. The drug was used often without reaction in patients who had had untoward reactions with other arsenical preparations.

The experimental use of clorarsen indicates that it is effective in acute syphilis, is attended by few reactions, and may be used as an alternate drug in patients having reactions to other arsenical drugs.

Using the same drug in the treatment of 96 syphilitics with a total of 2033 injections, Long<sup>9</sup> found that: (1) Healing of all lesions both early and late was rapid and complete; (2) there was no instance of clinical or infectious relapse; (3) the rapidity of the serologic reversal was on the whole satisfactory, and (4) there was a low incidence of abnormal spinal fluids among the patients with early syphilis. In the group of patients with manifestations of late syphilis, tolerance has been good, symptomatic improvement has been noted, and the results have been entirely satisfactory. Toxic reactions were few. Guy, Goldmann, and Gannon,<sup>10</sup> in a preliminary report, concluded that *phenarsine hydrochloride* (clorarsen) may prove to be more stable than, and compare favorably with (as to administration, toxicity, and early reports), other drugs depending for their efficacy on arsenoxide.

### Complications of Antisyphilitic Therapy in Pregnancy

Two deaths due to hemorrhagic encephalitis in pregnant women resulting from the use of an arsenical compound

prompted Kennedy and Henington<sup>11</sup> to study the whole question of the treatment of syphilis in pregnancy.

This investigation dates back to January 1, 1937, and the material includes all clinic patients receiving antisyphilitic therapy, all patients admitted to the hospital with complications following treatment and, for comparison, all obstetric deaths and all nonpregnant women of the same age group (20 to 35 years) under treatment in the same clinic. No distinction was made between Negro and white patients. The pregnant women were divided according to the trimester of pregnancy in which treatment was begun. Fatal cases are reported in detail.

The authors' results show that the most unfavorable time for treatment is in the last trimester, the rate of reactions rising sharply as pregnancy progresses. In a large percentage of all the cases of arsenical encephalitis reported in the literature the patients were pregnant women, most of them, as in the authors' cases, being in the last few months of pregnancy.

**Comment**—Castallo<sup>12</sup> and Rakoff and Cole and others have stated that pregnant women with negative serologic reactions should always be given antisyphilitic therapy when there is a past history suggestive of syphilis, such as repeated premature deliveries, a macerated fetus or stillbirth, when there is a history of a previous positive Wassermann reaction, when the paternal Wassermann reaction is positive, or when previous clinical signs of the disease have been elicited. Every syphilitic mother, irrespective of the amount of therapy she has received in the past, should receive treatment. In addition, she should be treated for the following reasons:

A. *Because of the Pregnancy*—1. Prematurity is 52.3 per cent higher in

untreated patients. It is reduced to one-half by treatment early in pregnancy. It is reduced to one-quarter by treatment both before and during pregnancy. 2. Breech presentation occurs in 13.8 per cent of untreated syphilitic mothers, or at three times the normal rate. 3. The birth rate is only one-half as high for untreated syphilitic women as for the general population, the rate for syphilitic women being 2.05 per cent and that for the general population 3.8 per cent.

**B. *Because of the Child***—1. If the woman is treated before the fourth month of pregnancy, a healthy baby is almost assured (syphilis is not found on serial sections before the fourth fetal month). 2. Stillbirths occur in 8.3 per cent of untreated syphilitic mothers. 3. Miscarriages occur in 13.1 per cent of untreated obstetric patients. 4. Congenital syphilis can be prevented in cases of mothers with primary or secondary lesions. 5. Thirteen and one-tenth per cent of the babies of untreated women die before leaving the hospital. Only 2.9 per cent of the infants of treated patients die. 6. The rate of death for syphilitic children is 8 to 10 per cent, and the mortality after leaving the hospital is 25 to 48 per cent.

**C. *Because of the Syphilis Itself***—1. Syphilis should be treated, especially in its early stages, because it is a contagious and infectious disease. 2. The opportunity of treating the syphilis is presented, since the patients will return for obstetric check-ups.

It is of interest here to mention the long term results studied by Padget in the treatment of early syphilis. The influence of sex on the outcome of the treatment is apparent. Of parous women, 70 per cent were cured; of nulliparous women, 65.4 per cent were cured, and of men, 60.8 per cent were cured, these

figures substantiating the idea that pregnancy has a beneficial effect on syphilis. One seldom sees multipara with syphilis of the central nervous system.

Pregnant women with syphilis are not treated if one of the following conditions exists: 1. Asymptomatic syphilis is detected too late in pregnancy. The treatment is not of any great benefit to the child, and it may temporarily mask a syphilitic infection in the child, besides endangering the life of the mother. 2. There is toxemia of pregnancy, with already overloaded kidneys. 3. There is a history of severe reactions to arsenical compounds or of sensitivity to drugs.

### **Treatment of Syphilis in Pregnancy**

The authors believe, in general, that the dose of the arsenical compound should be smaller than would ordinarily be used with a nonpregnant woman. It has been shown that the placenta stores arsenic, and it may be for this reason that smaller doses are effective.

**First Trimester** If the pregnancy is normal treatment should be begun as soon as the disease is discovered. The combined method, or as some prefer, alternating courses of 8 to 10 injections of the *arsenic* compound with 6 to 8 injections of a *bismuth* compound should be employed, the treatments being arranged so that the arsenic medication is given in the last few months.

**Second Trimester** The treatment should be the same as that in the first trimester.

**Third Trimester**—The arsenic or bismuth compound should be used in the seventh month and the bismuth preparation and *iodides* in the eighth and ninth months. Arsenic medication should not be employed unless the patient has primary or secondary or otherwise active syphilis and one wishes to disinfect the patient and prevent congenital syphilis.



### Mapharsen in the Treatment of Congenital Syphilis

The various therapeutic plans that have been used in the treatment of congenital syphilis have not proven too satisfactory, particularly as regards the treatment of interstitial keratitis and the effect upon the blood Wassermann reaction. New ideas on the treatment of congenital syphilis are therefore scanned carefully. To say that the use of mapharsen in this regard is new is not exactly correct, as it has been tried for congenital syphilis almost since its introduction, but a review of the recent thorough study undertaken by Astrachan and Cornell,<sup>13</sup> and in an evaluation of this trivalent arsenical. They conclude "that *mapharsen* is a useful drug in the treatment of late congenital syphilis," and it may be safely said that late congenital syphilis is a much more difficult therapeutic problem than infantile congenital syphilis. Injections were given intramuscularly to some patients, intravenously to others, and in some instances were supported by injection of *bismuth* compounds.

In 55.5 per cent of their cases the blood serologic reaction reversed partially or completely. This percentage is a fairly good one in cases of late congenital syphilis, in which in not less than 50 per cent of instances there is a fixed serologic reaction, regardless of treatment given. The fact that improvement occurred in all six cases of interstitial keratitis following mapharsen therapy emphasizes its value in cases of late congenital syphilis.

In a previous contribution a preference was expressed for the concurrent method of administration of bismuth compounds and mapharsen when dealing with cases of late congenital syphilis. With regard to this problem an analysis of the serologic response in the authors' cases showed that there were more im-

proved cases among those treated with the concurrent method (mapharsen and bismuth together) (58.8 per cent) than among those treated with the alternate method (mapharsen and bismuth alternately) (53.5 per cent). The concurrent method was used more among the improved cases (40 per cent) than among the unimproved ones (35 per cent). Although the difference in percentages is a very small one, it still points to a favorable influence of the concurrent method on the effectiveness of mapharsen therapy.

Four of the authors' cases showed an improvement only when the concurrent method was used; this also points to the advisability of the use of this method. On the other hand, the concurrent method is more liable to cause untoward reactions than the alternate one. For this reason the concurrent method should be used only for healthy patients and it should be combined with the alternate method of administration, that is, a course of bismuth and mapharsen given concurrently should be followed by courses of bismuth and mapharsen given alternately. It is also imperative that the patients be carefully observed and frequent blood counts and liver function tests be done.

As to the question of the lower toxicity of mapharsen in comparison with other arsenicals, the authors stress the absence of exfoliative dermatitis, nitritoid reactions, the small number of immediate and delayed reactions in this series, and the fact that several of the patients who were sensitive to neoarsphenamine tolerated mapharsen well

### Technic of Darkfield Microscopy

The following technic for darkfield microscopy is recommended by Witlin<sup>14</sup> as a standard procedure: Lower the substage and place a drop of cedar oil, free of bubbles, on the upper surface of the

condenser. Put the slide preparation on the stage and center the specimen. Raise the substage until the oil is spread by contact with the slide, filling the space between the slide and condenser. Examine under low and high power followed by the oil immersion objective. *Do not place cedar oil on top of coverslip until ready for the oil immersion observations.* By employing the low and high dry objectives, time is saved in locating the organism, and in most instances adequate results for diagnostic purposes are provided. As a further check on an organism under view the microorganism may be centered in the microscopic field, a drop of cedar oil placed on the coverslip and examination made with the oil immersion objective.

### Effects of Smallpox Vaccination (Vaccinia) on Serologic Tests for Syphilis

It has long been known that smallpox vaccination may cause a falsely positive serologic test for syphilis and this was observed by numerous physicians during the widespread vaccinations practiced during the winter of 1942 and 1943. The observations of Favorite<sup>15</sup> on this subject are of interest. A group of 202 medical students and nurses known to have negative serologic reactions were vaccinated and repeatedly tested using Kolmer, Kahn, and Mazzini tests. Twenty-four persons (11.8 per cent) were seropositive at one time or another following the vaccination. The patients with positive reactions were re-tested every two weeks. There was a gradual diminution in the intensity of the reactions until all became negative by the end of 120 days.

### Oral Manifestations of Bismuth Therapy

Compared with the oral manifestations

that resulted from the employment of mercury in the treatment of syphilis, those following bismuth therapy are far less common and less severe. The prevalence of pigmentations in the mouths of patients referred to the dental clinic suggested to Dean<sup>16</sup> that more attention should be given to the oral condition of patients receiving antisypilitic therapy.

The dark line on the gums and other symptoms, such as bleeding of the gums, excessive salivation, a bad odor of the breath, puffing and swelling of the gum tissue, and occasional loosening of the teeth, were seen in the mouths of most of the patients receiving the bismuth treatments. The general dental service rendered at the clinic consisted of scaling and polishing of the teeth, treatment of the gums, placing of amalgam and synthetic porcelain fillings, and extractions. These services resulted in such marked improvement in the mouths that test cases were selected for study.

The test cases were developed by administering the general dental service on one-half of the lower jaw of patients showing symptoms of bismuth stomatitis. The other half of the lower jaw was not treated and served as a control. Careful records were kept and in a majority of cases favorable results were obtained. Specific recommendations were made to the patients regarding home care of the mouth, such as the use of a hard bristle toothbrush at least twice daily, massage of the gums with the fingertips at regular intervals throughout the day, and the use of a mouthwash.

From analyses of the black deposit it was believed that the deposit is probably bismuth sulfide, resulting from the presence of sulfur in the mouth due to decomposition of food and the presence of sulfur in the body cells.

The author believes it is not necessary to interrupt or to discontinue the use of



bismuth solution because of oral manifestations in the treatment of syphilis, if adequate dental service is given before or during the periods of injections. The elimination of the bismuth pigmentation by the dentist improves the appearance of the patient and so leads to better co-operation from the patient in regard to treatment.

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## DIET AND DIET THERAPY

DEACONESS MAUDE BEHRMAN, B.S.

### INTRODUCTION

A survey of literature in the year 1943 for material which emphasizes work done along special diet lines may seem rather useless. Treatment by diet of certain diseases continues along lines laid down for many years past. A review of recent thoughts on the treatment of the diabetic is given, but there is comparatively very little new. The article which is included on rationing and the need for special food for special diets, is rather interesting since it reviews and brings to mind the many diets still used and found effective in the treatment of disease. The use of the ketogenic diet for epilepsy is nothing new, but the diet as outlined in the article is so simple and easy to follow that the reviewer thought it would make it easier for the physician to plan such a diet, should he have occasion.

Nutritional problems in war time present the one big problem: Undernour-

ished boys going into service, fatigue in defense plants due to improper feeding, lack of energy after the day's work is done, and the delay in production due to improper feeding, resulting in absenteeism. These and many more reasons have brought the subject of nutrition out where it is now classified as a subject worth so much that governments are willing to have representatives meet together, to discuss for days the problem of feeding the world after this war is over.

Conditions today are increasing the need for certain foods for many people. With rationing, some people are not willing to study the situation and deal with it wisely. They are doing without and wrecking their health. There will be sickness as a result of malnutrition and undernourishment. Everyone should review and study the list of protective foods which should be included in the

daily dietary of every individual. Bar-borka<sup>1</sup> lists them as follows:

Milk .. .....1 pint for adults, 1 quart for children  
 Egg .....1  
 Vegetables .....3 large servings besides potato (1 green leafy)  
 Fruit .....2 servings (1 raw)  
 Meat, fish, or fowl .....1 serving (about 2 oz.)  
 Butter .....1 tablespoonful  
 Wholegrain products and enriched bread are needed every day.

**EXAMPLE:**

Cereal .....Wholegrain or enriched (1 serving)  
 Bread .....Wholegrain or enriched (3 slices)

Then eat the additional foods as preferred.

If the above is taken, it contains approximately 1800 to 2000 calories, 70 Gm. of protein, 0.93 Gm. of calcium, 22 mg. iron, 6105 units of vitamin A, 1.8 mg. of thiamin, 2.3 mg. of riboflavin, and 129 mg. of ascorbic acid. With the possibility that more food will be eaten, this diet should meet the recommended requirements as follows:

For a man of 70 kg., moderately active: 3000 calories, 70 Gm. of protein, 0.8 Gm. of calcium, 12 mg. iron, 5000 units of vitamin A, 1.8 mg. thiamin, 75 mg. ascorbic acid, 2.7 mg. riboflavin, 18 mg. niacin.

Illness, increased working hours, extremes of temperature, perspiration, speedup, insufficient rest may all tend to increase these needs.

The working efficiency of employees in defense industries is giving nutrition workers some concern. A study of their dietary habits has shown very poor results. If their inadequate diets can be brought up to adequate diets, then there will be greater production of work and fewer accidents.

Foods should be provided for these defense workers. Diets of natural foods should be emphasized. Supplementing

the diets of defense workers with vitamin concentrates does not make sense. Bar-borka does not believe in the administration of vitamin concentrates when an adequate diet is available as it still is in this country. This statement does not apply to the individual who is unable to take the adequate diet due to some disease.

### Can We Eat Our Way to Health or Disease?

Fishbein<sup>2</sup> said before a meeting of the Fifth Annual Congress on Industrial Health that the scientist who has devoted himself to a study of nutrition is very careful to say "that sound nutrition depends primarily on proper selection, preparation, consumption, and absorption of foods, because only by eating foods as a whole can we be certain to secure the necessary amounts of substances which may be still unknown, and which may play a vital part in human nutrition. He refers to the postwar planning in restoring sound nutrition to the peoples of the world who have suffered as a result of the war. It is the hope of Dr. Fishbein that the governmental agencies concerned with feeding the starving world will get the advice of scientific bodies capable of making "scientific diagnoses of nutritional needs in order that the treatment be reasonably specific."

He deplores the indiscriminate use of vitamins by the public and hopes that the time will come when the public will realize that the vitamins for the treatment of disease should be left wholly as a professional problem. The articles which the Council on Foods and Nutrition of the American Medical Association have been publishing seem to be worth while and, as he says, deserve repetition.

1. We are a careless people. We fortify our foods with riboflavin; then

we leave a bottle of milk standing in the sunlight for an hour so that it loses most of that vitamin.

2. We shop carelessly, selecting our foods for the pictures on the packages rather than with a knowledge of their actual food values.

3. We prepare food carelessly; fruit cut for salad or cabbage shredded for cole slaw loses one-fourth of its vitamin C by standing exposed to the air hours before use.

4. We cook our foods into food deficiencies, throwing away the water from vegetables and destroying vitamin values by long heating.

5. Oleomargarine, suitably enriched with vitamin A, is a good source of fat in the diet. However, it is just oleomargarine enriched with vitamin A. We are not yet certain that it is in every way equivalent to butter.

6. The old idea that fats were unnecessary in the diet is no longer acceptable. New standards suggest that we eat about the same number of calories in fats as in carbohydrates and that about 15 per cent of the diet must be protein. We should regulate the quantity of food to the amount of energy required and make certain that food taken in these amounts supplies the essential substances of which we now have knowledge.

7. The problems of infancy and old age related to nutrition are special problems. Old people do not eat properly in relation to their diminished output of energy, neither do they select the necessary ingredients. Proper nutrition for old people might give us a greater number of men and women beyond 60 years of age capable of standing erect, working efficiently, and more free from the aches and pains which were formerly accepted as an inevitable accompaniment of the sixth and seventh decades of life.

8. Nobody knows how many factors actually constitute the vitamin B complex. There are at least 12. The evolution of our knowledge of this vitamin can serve as an example of the manner in which we are progressing and of the danger of drawing conclusions that are too hasty, in relation to essential substances.

9. Indiscriminate mixtures of vitamins and minerals have never been approved by any scientific body in the field of nutrition. When the Council on Foods and Nutrition announced its action regarding mixtures, it recognized the necessity for such mixtures as the vitamin B complex. It did not approve and has never approved mixtures with all the known vitamins and extra minerals.

10. The human being is constituted with a stomach and some 30 feet of intestines which require food for their functional efficiency. Man is not made for a diet of pills and capsules.

### **Dietary Recommendations for Blood Donors**

Questions from blood donors about information concerning the best foods for blood regeneration brought about this study by Turner.<sup>3</sup> The preparation of the material was done by a Committee of the Diet Therapy Section of the American Dietetic Association. McKibben and Stare conclude: "It is evident that nutrition is of importance in blood regeneration and that good nutrition favors rapid regeneration. It would seem that foods rich in iron and protein in the average diet of the average blood donor will generally ensure a more rapid return of the blood picture to normal. As a measure of safety, the diet should also include liberal amounts of other essentials, such as copper, as well as those factors whose relation to blood

regeneration in man has not been clearly established, namely, some of the vitamins of the B complex. In general, a diet fully meeting the requirements of the Food and Nutrition Board of the National Research Council, with increased emphasis on iron and protein foods, can be expected to provide optimum blood regeneration."

Patterns for the daily menu have been planned and follow the above principles very closely. Even though the minimum amounts of the protective foods recommended in the menu plan are used by the blood donor, the diet will conform to the daily allowances recommended by the Food and Nutrition Board for calcium, iron, vitamin A, thiamin, ascorbic acid, riboflavin, and niacin. The protein, chiefly good quality proteins, and proteins that are rich sources of iron, will average 75 Gm. daily. Suggestions for additional sources of iron—rich foods are also included.

**Pattern for Daily Menu Plan—Meat, Poultry, Fish or Soybeans—**Approximately 4 ounces daily (edible portion). Include liver or kidney in the diet 2 or more times per week. Lamb, beef, calf, or pork liver may be used. Liver should be cooked only until it is no longer red. Beyond that point, it becomes tough. Heart and tripe are also good blood builders.

Pork or ham once per week will augment the thiamin intake. Other meats, poultry, and fish may be used as desired. Oysters are of especial value.

Soybeans have been found to contain proteins of good quality and quantity. One-half cup of cooked soybeans is equivalent to approximately 2 ounces of edible meat.

Recipes for the use of soybeans may be obtained from the Bureau of Home Economics and Human Nutrition, U. S. Department of Agriculture, Washington,

D. C., and from the Department of Home Economics, University of Illinois, Extension Service in Agriculture and Home Economics, Urbana.

**Eggs**—One or more daily. Eggs may be used alone or combined with other foods. Soybeans may be used as a substitute for eggs in the following proportion: One-half cup of cooked soybeans is equivalent to two eggs.

**Milk**—One pint or more daily. It may be used for cooking and for drinking. One ounce of American cheese may be considered approximately equal to one glass of milk (7 ounces) in calcium, phosphorus, iron, and protein. However, the thiamin and riboflavin values will be considerably less in the cheese portion.

**Legumes**—Two or more servings per week of soybeans, dried peas, beans, lentils, or peanut butter.

**Fruit**—Two or more servings daily, of which one should be a larger serving of citrus fruit or tomato, either fresh or canned. Apricots, peaches, and prunes have been found to be effective blood builders and may be used as the second fruit.

**Vegetables**—Two or more servings daily, one of them leafy green or yellow. In addition, use one or more servings of either white or sweet potato daily. In cooking vegetables, use a small amount of water where possible and cook for a short period of time. The water in which vegetables are cooked should be saved and used in soups, gravies, and "vegetable cocktails."

**Cereals and Breads**—Whole-grain or enriched cereals and whole-grain or enriched white bread should be used daily. These foods may be used in amounts necessary to meet caloric requirements.

**Fats and Sweets**—These foods may be used in addition to the protective foods listed above, but not as a substi-



whose metabolism was supposedly normal. Out of ten cases, eight showed plasma cholesterol unaffected by diet. The other two showed a definite rise in the blood cholesterol by the addition of 900 mg. of cholesterol a day and the addition of three eggs to a basic diet. The method of determination was the colorimetric method of Myers and Wardell. When the digitonin-precipitation method of Okey was used on ten patients, not one case reported showed an elevation of plasma cholesterol.

### The Diet in Diabetes Mellitus

While Cutting and Robson<sup>5</sup> have nothing new to discuss, it is worth while and may bring back to mind some interesting phases of diet in diabetes which have been neglected in recent years. After a brief review of diets used in pre-insulin days, the authors say that, due to the higher carbohydrate intake which has been made possible by the availability of insulin, there may be a tendency toward the use of unlimited or "free" diets. This is deemed unwise, since most diabetic patients are most willing to follow a prescribed diet when they understand how to do it. When planning the diabetic diet, the diet habits of the patient should be followed as nearly as possible. Correction of certain undesirable food habits may be necessary. The diabetic diet should be "consistent with the following aims: (1) To make the constituents of the diet those foods which the patient usually eats; (2) to keep the total calories, carbohydrate, protein, and fat relatively constant from day to day; and (3) to correct any defects which may appear in the patient's accustomed diet."

The method of constructing the diabetic diet which follows is that procedure which is followed in the Stanford Metabolic Clinic.

The caloric value of the diet should be enough to keep the patient at normal weight. Fifteen hundred calories will usually keep a person at normal weight. Of course, a lot depends on the type of activity. A person doing very hard manual labor may need twice the amount. A person who is underweight needs more calories and also extra insulin. Sometimes, it has been found that obese patients become sugar free when they lose weight on a reduction diet. The suggestion is made that obese persons who are diabetic should not be given insulin until they lost enough weight to be normal. The sugar loss in the urine will increase the weight loss. If there are serious symptoms other than obesity, then they should be given insulin. As soon as the normal weight is reached and glycosuria is still present, then insulin must be given.

The protein requirement is next determined. The usual amount is given, that is, 1 Gm. per Kg. of body weight or approximately 75 Gm. for a normal adult. This will yield 300 calories.

The remaining calories are made up now. Most persons usually eat twice as much carbohydrate as fat. If this is followed, then each type of food will yield approximately the same number of calories, since 1 Gm. of carbohydrate yields 4 calories and 1 Gm. of fat, 9 calories.

An example of how the diet prescription is worked is then given as follows:

"If a diet of 2000 calories is desired for a person of correct body weight, doing light work, 300 calories should come from protein (or 75 Gm.), leaving 1700 calories to come from carbohydrate and fat. One-half of this, or 850 calories may come from carbohydrate (212 Gm.); and one-half from fat (95 Gm.). The diet prescription made out by the physician then becomes calories, 2000:

protein, 75 Gm. carbohydrate, 213 Gm.; and fat, 95 Gm."

This diet prescription should then be given to a dietitian to work out into three well balanced meals, adequate in everything including vitamins and minerals. Not all physicians have a dietitian available. Sample diets are listed below to aid the physician who needs some help in planning diets for his patients. These may be mimeographed and will help a great deal. If other diseases complicate diabetes, then the diet must be adapted to the complication. Patients who have peptic ulcer need a smooth diet. The same diet may be given except that rough foods will be eliminated and vegetables and fruits and coarse cereals will be strained. A high caloric diet is given to the patient who is tuberculous. Nephritis may mean a reduction in the protein intake with the calories made up in carbohydrate.

The sample diet forms which are used by Cutting and Robson are given here:

#### I. REDUCING DIET: 960 CALORIES

CARBOHYDRATE, 80 GM.; PROTEIN, 70 GM.;  
FAT, 40 GM.

##### *Breakfast*

Fruit—1 serving; cereal—1 tablespoon (dry measure before cooking); bread—1 slice; egg—1; skim milk—1 standard measuring cup (or canned milk— $\frac{1}{2}$  cup).

##### *Lunch and Dinner*

Lean meat, fish or fowl—1 small serving, or cheese—1 small slice, or cottage cheese—2 heaping tablespoons, or eggs—2; vegetables—2 generous servings (2 cups); skim milk—1 standard measuring cup (or 1 cup buttermilk); fruit—1 serving (1 grapefruit, 1 orange, 1 cup berries,  $\frac{1}{4}$  slice watermelon (across),  $\frac{1}{2}$  small cantaloupe, 1 pear, 1 peach, 3 apricots, 2 plums, 1 small apple, 1 small banana,  $\frac{1}{2}$  cup orange juice or  $\frac{1}{2}$  cup pineapple juice, 1 cup tomato juice or 1 cup grapefruit juice, or  $\frac{1}{2}$  cup dried stewed apricots or  $\frac{1}{2}$  cup dried prunes, stewed without sugar).

MAY TAKE: Clear soup, plain tea or coffee with any meal. Saccharin, 0.0025 Gm. ( $\frac{1}{4}$  gr.) may be used for sweetening if desired. Liquid

petrolatum (mineral oil) may be used to replace fats and oils, as in salad dressings.

AVOID: *Bread* in any form except as stated above, including gluten bread, melba toast, crackers, Rye Krisp and advertised "reducing breads."

*Starchy Foods*: Rice, noodles, potatoes, beans, corn, peas.

*Sweets*: Honey, jam, candy, and all desserts.

*Sweet Fruits*: Prunes, grapes, persimmons, cherries, figs, and all fruits canned with sugar.

*Fats*: Gravy, salad dressing, mayonnaise, oil, cream, butter, lard, avocado.

Vitamin capsules (polyvalent) daily as prescribed (usually 2).

#### II. DIET: 1530 CALORIES

CARBOHYDRATE, 150 GM.; PROTEIN, 75 GM.;  
FAT, 70 GM.

##### *Breakfast*

Fruit—1 serving; cereal—1 tablespoon (dry measure before cooking); milk—1 standard measuring cup or  $\frac{1}{2}$  cup canned milk; bread—1 slice; butter—1 square; egg—1.

##### *Lunch*

Lean meat, fish, or fowl—1 small slice (1 oz.), or cheese—1 small slice, or cottage cheese—2 heaping tablespoons, or egg—1; vegetables (raw or cooked)—2 generous servings (2 cups); fruit—1 serving; bread—1 slice; butter—1 square, or mayonnaise or oil—2 teaspoons; milk—1 cup.

##### *Dinner*

Lean meat, fish, or fowl—1 medium serving ( $\frac{1}{4}$  pound raw); potato—1 small (size of egg), or bread—1 slice, or noodles, rice, corn, or beans— $\frac{1}{2}$  cup; vegetables—2 generous servings (2 cups); butter—1 square; fruit—1 serving ( $\frac{1}{2}$  grapefruit, 1 small orange, 1 cup fresh berries (no loganberries),  $\frac{1}{2}$  cantaloupe,  $\frac{1}{2}$  slice of watermelon (1 $\frac{1}{2}$  inches thick), 3 apricots, 1 small peach, 2 plums, 2 thin slices of fresh pineapple,  $\frac{1}{2}$  medium apple, 3 nectarines,  $\frac{1}{2}$  medium pear, 2 figs,  $\frac{1}{2}$  banana, 1 cup grapefruit juice, 1 cup tomato juice,  $\frac{1}{2}$  cup orange juice,  $\frac{1}{2}$  cup pineapple juice,  $\frac{1}{4}$  cup dried cooked apricots or prunes, when stewed without sugar).

MAY TAKE: Clear soup, plain tea and coffee with any meal. Saccharin, 0.0025 Gm. ( $\frac{1}{4}$  gr.) may be used for sweetening, if desired. Any kind of bread may be used, but only in the amounts specified.

AVOID: Sweets, such as sweetened canned fruit, honey, sugar, all desserts, and fruits which are not listed here.



It is important not to eat larger helpings than those listed here.

### III. DIET 2062 CALORIES

CARBOHYDRATES, 220 GM.; PROTEIN, 93 GM.;  
FAT, 90 GM.

#### Breakfast

Fruit—1 serving; cereal—3 tablespoons (dry measure before cooking); milk—1 standard measuring cup (or  $\frac{1}{2}$  cup canned milk); bread—1 slice; butter—1 pat; egg—1.

#### Lunch

Meat, fish or cheese or eggs—1 small serving ( $\frac{1}{8}$  pound equals 2 oz.); vegetables (raw or cooked)—1 generous serving (1 cup; bread—2 slices; butter, mayonnaise, or oil—2 pats, or 4 teaspoons; fruit—1 serving; milk—1 cup.

#### Dinner

Lean meat, fish, or fowl—1 medium serving ( $\frac{1}{4}$  pound raw); potato, or bread—1 medium, or 2 slices; vegetables (raw or cooked) except corn, beans, peas—1 generous serving (1 cup); butter, mayonnaise, or oil—2 pats, or 4 teaspoons; fruit—1 serving (2 oranges or 1 cup juice, 1 large grapefruit or 1 cup juice, 1 small cantaloupe, 2 cups fresh berries, 1 slice watermelon (2 inches), 7 apricots, 1 large peach, 1 slice canned (sweetened) pineapple, 1 cup pineapple juice, 6 plums, 1 apple, 1 medium bunch grapes ( $\frac{1}{2}$  pound), 6 nectarines, 1 pear, 30 cherries, 4 figs, 1 small persimmon, 1 banana, 5 prunes, or  $\frac{1}{2}$  cup stewed dried fruit, cooked without sugar).

Instead of one serving fruit,  $\frac{1}{2}$  cup jello, custard, or junket may be used occasionally.

Instead of 1 medium potato, the following may be used: 1 cup green peas, 2 medium ears fresh corn or  $\frac{3}{4}$  cup canned corn, or  $\frac{3}{4}$  cup cooked beans, rice, noodles, or macaroni.

MAY TAKE: Clear broth, plain tea or coffee with any meal. Saccharin ( $\frac{1}{4}$  grain) may be used for sweetening, if desired.

AVOID: Sweets, such as sweetened canned fruit, honey, sugar, and desserts. Eat all listed for breakfast, lunch, and dinner, but only in the amounts prescribed.

### IV. DIET: 2550 CALORIES

CARBOHYDRATE, 295 GM.; PROTEIN, 95 GM.;  
FAT, 110 GM.

#### Breakfast

Fruit—1 serving; cereal—2 tablespoons, or fruit—1 extra serving; milk—1 standard measuring cup (or  $\frac{1}{2}$  cup canned milk); bread—2 slices; butter—2 pats; egg—1.

#### Lunch

Choice of:

1. Meat or cheese or egg—1 slice, or 1; vegetables (except potatoes, corn, peas, beans)—1 cup; rice or noodles— $\frac{3}{4}$  cup; bread—2 slices; butter—2 pats, or oil or mayonnaise—4 teaspoons.

2. Macaroni and cheese or similar creamed dish; or canned beans, lima beans, peas or corn— $\frac{3}{4}$  cup; vegetables (except as noted above)—1 cup; bread—2 slices; butter—2 pats, or oil or mayonnaise—4 teaspoons.

3. Meat or cheese or egg—1 slice, or 1; vegetables, raw or cooked (except as noted above)—1 cup; bread—4 slices; butter—2 pats, or oil or mayonnaise—4 teaspoons; fruit—1 serving; milk—1 cup.

#### Supper

Lean meat, fish, or fowl—1 medium serving ( $\frac{1}{4}$  pound raw); potato—1 serving (medium), or bread—2 slices; vegetables (except as noted above)—1 cup; butter—1 pat; salad oil or mayonnaise—1 tablespoon; milk—1 cup; fruit—1 small serving or occasionally ice cream, pudding, or unfrosted cake.

#### Bedtime Nourishment

Fruit—1 serving (2 oranges or 1 cup juice, 1 large grapefruit or 1 cup juice, 1 small cantaloupe, 2 cups fresh berries, 1 slice watermelon (2 inches thick), 7 apricots, 1 large peach, 1 slice canned (sweetened) pineapple or  $\frac{1}{2}$  cup canned (sweetened) peach or pear, 1 cup pineapple juice, 6 plums, 1 apple, 1 medium bunch grapes ( $\frac{1}{2}$  pound), 6 nectarines, 1 pear, 30 cherries, 1 banana, 5 prunes, or  $\frac{1}{2}$  cup cooked (without sugar) dried fruit.

USE AS DESIRED: Clear soup, or plain tea or coffee.

Measure all serving. Do not overeat. Avoid concentrated foods such as candy, honey, jam, syrup, and sugar.

## The Diet in Epilepsy

Under Current Comment<sup>6</sup> in the *American Journal of Dietetics*, an article of Peterman is discussed and some sample menus and instruction lists are given for children who suffer attacks of epilepsy. The diagnosis is most important. He says that whenever possible the diagnosis of idiopathic epilepsy should be confirmed or established with an electroencephalogram. If, after this, the child



does not respond to treatment, then a pneumoencephalogram should be made.

One investigator found that 90 per cent of the children with normal pneumoencephalograms responded well to treatment with the ketogenic diet. The diet is not a difficult one, but it is expensive due to the large amount of fats, such as cream, bacon, and butter. The diet should be preceded by a ten-day fast during which orange juice, diabetic broth, and bran wafers (no food value) are given. A total of 200 cc. juice, 400 cc. broth, and 400 cc. water is allowed daily with as many bran wafers as desired. The patient is then started on a diet consisting of 15 Gm. of carbohydrate, 1 Gm. of protein per Kg. of body weight, with the remaining caloric requirement in fat. The daily allowance is 15 calories per pound but does not need to exceed 2000 calories.

Following is a summary of instructions which are given for the diets of the epileptic children. Nell Clausen, of the Milwaukee Children's Hospital, has prepared them:

A gram scale is absolutely necessary.

Add to the diet nothing containing available carbohydrate, protein, or fat which is not included in the calculated diet chart.

Include one egg daily.

Use 300 Gm. of cream daily if possible to ensure a supply of calcium and phosphorus.

Use some raw fresh fruit and one cooked and one fresh vegetable daily to protect against mineral and vitamin deficiencies.

Bran wafers, diabetic bran breakfast food, and "D-Zerta" may be used *ad lib.*

Broth may also be added but must be deducted from fluid allowance.

#### KETOGENIC DIET FOR FIVE-YEAR-OLD CHILD

##### Breakfast

30 Gm. sliced orange	100 Gm. 30% cream
13 Gm. butter	May have "cellu" bran
1 egg in omelette	breakfast food

##### Dinner

30 Gm. spinach	50 Gm. cream in ice
10 Gm. butter	cream (whip cream
20 Gm. scraped beef	and flavor with ¼
pattie	tsp. vanilla and ½ gr.
50 Gm. cream to drink	saccharin)
	May have bran wafers

##### Supper

Celery soup (50 Gm. cream, 20 Gm. celery, 10 Gm. butter)	"D-Zerta"
50 Gm. asparagus	Fluids, 300 Gm. (1000
6 Gm. butter	cc. — 300 cc. = 700
50 Gm. cream	cc. to be allowed between meals)

#### KETOGENIC DIET FOR TEN-YEAR-OLD CHILD

##### Breakfast

30 Gm. fresh pineapple	100 Gm. 30% cream
20 Gm. butter	May have "Cellu" bran
1 egg scrambled with cream and butter	breakfast food

##### Dinner

50 Gm. broiled tomato	in mushrooms)
20 Gm. butter	75 Gm. cream to drink
70 Gm. steak with mushrooms (no available fuel value	"D-Zerta" with 25 Gm. whipped cream

##### Supper

Vegetable soup (50 Gm. broth, 10 Gm. celery, 3 Gm. onion, 4 Gm. carrot, or 20 Gm. 3% vegetable)	100 Gm. cream in coa (100 Gm. cream, ¼ teaspoon cocoa, ½ gr. saccharin)
20 Gm. butter	Fluids, 350 Gm. (1000
20 Gm. raw cabbage with 12 Gm. mayonnaise	cc. — 350 cc. = 650
20 Gm. bacon	cc. water to be allowed between meals)

If convulsions continue, then 5 Gm. of fat must be added to the daily allowance every week to the limit of tolerance.

When the convulsions are under control, the child should remain on the diet as it is for three months. After that, 10 Gm. of protein may be added to the daily allowance. If no convulsions appear, then 10 Gm. of carbohydrate may be added to the daily intake after the

next month. This can be done alternating between carbohydrate and protein every month, until the protein reaches 2 Gm. per Kg. of body weight. After six months, the fat allowance may be reduced by 10 Gm. every month. The menus should be divided into three equal meals at well spaced intervals. Only water is given between meals.

### Special Diets Under Rationing

Adlersberg and Hauser<sup>7</sup> discuss the need of rationed foods in special diets. There are still plenty of unrationed foods and there should be no excuse for the diet of most persons and for most pathological conditions being inadequate. Requests are coming in to physicians and dietitians for extra allowances of special foods; therefore, it seems to be a good

time to review the material which is discussed.

Clinics of many hospitals, the chiefs and staff members were interviewed with results shown in Table I.

A discussion of the various conditions which may need extra allowances are included here, practically word for word, because the reviewer feels that they are valuable discussions, not only from the point of view of rationing but also as a review of the variable needs of the certain foodstuffs in different diseases.

**Acute Infection**—This disease calls for a high caloric, high vitamin diet. Additional amounts of fats and sugar may be needed, and occasionally canned and processed fruits and fruit juices. The amounts requested will vary according to social, financial, and local factors.

TABLE I

Conditions in Which Extra Allowances of Rationed Foods Are Required*	Sugar Stamp	Red Stamps		Blue Stamps
	Carbo-hydrate	Protein (Canned Fish, Meat, Cheese [Hard])	Fat (Fats, Oils)	Canned and Processed Foods (Vegetables and Fruits)
Acute infection .....	yes	no	yes	yes (?)
Allergy .....	yes	yes	yes	yes (?)
Anemias .....	no	yes (?)	no	no
Cancer .....	no	yes	yes	no
Celiac disease .....	no	yes	no	no
Convalescence .....	yes	no	yes	no
Diabetes .....	no	yes (?)	yes (?)	yes (?)
Epilepsy .....	no	no	yes	no
Gastrointestinal disorders ...	no	no (?)	yes	no
Hypoglycemia (idiopathic) ..	no	yes	no	no
Liver disease .....	yes	yes (?)	no	yes (?)
Malnutrition .....	yes	no	yes	no
Nephrosis .....	no	yes	no	no
Obesity .....	no	yes	no	no
Skin (pemphigus) .....	no	no	yes	no
Thyroid disease .....	yes	no	yes	no
Vitamin deficiency .....	no	yes (?)	no	no

\* Conditions not listed are those which, in the opinion of the physicians interviewed, do not require additional allowances for the maintenance of adequate nutrition. Question marks indicate that extra allowances are required only in certain instances. See discussion in text.

**Allergy**—Every case of allergy is different from the other, therefore nothing definite can be said about needs. It stands to reason that if certain types of protein foods are not allowed, such as eggs and milk, then the rationed items, such as meat and canned fish, may have to be increased.

**Anemias**—Since liver extracts are satisfactory, it may not be necessary to ask for extra allowance of points for liver. Liver need only be served two or three times a week.

**Arthritis**—Since acute arthritis, chronic infectious arthritis, and arthritis deformans are satisfied with a simple, easily digested diet, no extra points are needed. Gout, obesity, malnutrition, and anemia are often associated with arthritis, but are discussed under these separate headings.

**Ash Diets (Acid, Alkaline, Neutral)**—These diets are used in conditions such as heart and kidney disease, arthritis, nephrolithiasis, etc. Present rations are ample for the alkaline ash and neutral ash diets. An additional allowance of meat may be necessary on the acid ash diet, because fruits and vegetables are limited and the diet is very high in protein.

**Cancer**—Cancer of the mouth, tongue, etc., may require a liquid diet, high caloric, high fat. Extra allowances of protein and fat are justifiable in incurable cancer.

**Celiac Disease**—A low carbohydrate, high protein, low fat diet is used in this disease as well as in tropical and non-tropical sprue. The very high protein requirement of this diet, usually between 150 to 200 Gm. per day makes it absolutely essential that an extra allowance be made for lean meats.

**Convalescence**—An extra allowance of calories in the form of sugar and fat may be necessary, but only for a period

of a few days or weeks or months as the case may be.

**Diabetes**—The average diabetic diet ranges around 150 to 250 Gm. of carbohydrate, 60 to 80 Gm. of protein, and 60 to 80 Gm. of fat per day. According to the views published recently by the New York Diabetes Association, these diabetics do not require an extra allotment. If the physician still prefers the high fat diet or the high protein diet or because of some abnormal condition associated with diabetes, then it may be necessary to modify the above statement.

**Epilepsy**—The ketogenic diet is still used by some physicians. This diet is very high in fat, and bacon, butter, and cream are essential. Heavy cream may be absolutely necessary.

**Gallbladder**—Since these diets are low in fat, an extra allowance is not needed.

**Gout**—The low purine diets which are also low in fat are used for gout, and no extra rations are needed.

**Gastrointestinal Disorders (Gastritis, Ulcer, Enteritis, Colitis)**—In gastrointestinal disorders, a high caloric intake is frequently indicated. An increased fat ration may be necessary, *e. g.*, in malnutrition, pyloric obstruction, etc. In cases of chronic diarrhea of any type, increased protein may be necessary to compensate for the loss of protein caused by hypermotility and poor absorption. In chronic conditions (carcinoma, ulcerative colitis), an extra allowance would be required almost indefinitely; in acute conditions, only for a few weeks.

**Hypoglycemia (Idiopathic)**—An extra allowance of meat and cheese may be necessary since patients with this disease usually do better on a high protein diet.

**Liver Disorders**—A high carbohydrate, low fat diet is still considered the best basic dietary treatment in most liver

disorders. If the daily carbohydrate quota goes over 400 Gm., then extra sugar may be needed and occasionally additional canned and processed fruits. Because of the known protective action of some of the amino acids, high protein diets are also frequently ordered, requiring additional meat and cheese; *e. g.*, in cirrhosis of the liver.

**Malnutrition**—In all conditions associated with malnutrition, a high carbohydrate, high fat, high caloric, high vitamin diet is given. Extra allowances of sugar and fat may be needed. The investigators feel that a diet up to 3000 calories does not need extra points, but those over 3000 will require extra sugar and fat.

**Nephritis (Nephrosis)**—An extra allowance of meat and cheese may be indicated when the patient is in the nephrotic stage of nephritis. There is no need for extra allowances to be made for the low protein diet.

**Obesity**—The low carbohydrate, low fat, high protein diet is the rule in cases of obesity. An additional allowance of protein may be necessary in the form of meat and cheese. Large amounts of the nonrationed foods, such as fish, poultry, and soft cheese, cannot be consumed.

**Postoperative Diets**—A diet of 3000 calories is usually ordered for patients who have had some surgery on the gastrointestinal tract. An extra allowance of sugar and fat may be necessary.

**Skin Disorders**—High caloric, high fat diets are indicated in some cases of skin disorders.

**Sprue**—SEE: celiac disease.

**Thyroid**—In cases of hyperthyroidism, increased sugar and fat quotas are desirable, as in other cases of malnutrition.

**Tuberculosis**—High caloric, high vitamin diet is indicated.

**Vitamin Deficiency**—Clear cut, primary deficiencies are comparatively rare in this part of the country. If encountered, they are usually secondary to some other systemic disease or alcoholism. If there is a mild vitamin deficiency, there should be no trouble in getting foods rich in vitamins A, C, and D. If a high protein diet is ordered to guarantee extra amounts of vitamin B complex, then extra allowance may have to be made.

**Social, Financial, and Local Aspects**—The social and financial situation of the individual, too, must be considered in determining whether present ration allowances will allow appropriate dietary treatment. For example, a high protein diet can easily be covered under the present rationing system if adequate amounts of nonrationed cheese, fish, shell fish, and poultry are consumed. The latter two items, however, are expensive and exceed the dietary budgets of low income groups. For similar reasons, diets requiring large amounts of fruit, fruit juices, and vegetables may justify an extra allowance of these items. Single individuals in lower income groups who work during the day frequently do not have time to purchase and prepare fresh fruits and vegetables daily. This is particularly true in the case of single men who have been accustomed to using large quantities of canned soups and vegetables because of lack of equipment and consequent difficulty in preparing even a simple meal, if it involves processes such as cleaning and cooking of fresh vegetables. Rural areas and small towns have always used less commercially canned foods than is customary in large communities like New York City. The high price of fresh vegetables in the New York area has been mentioned as one of the factors favoring the

use of canned and processed vegetables. Rationing boards should consider local conditions as well as individual circumstances when ruling on extra allowances due to disease.

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## ENDOCRINOLOGY

CHARLES W. DUNN, M.D.

### THE ADRENALS

**Adrenal Failure of Pituitary Origin**—Many of the serious symptoms of pituitary disease are of adrenal origin and a great deal can be accomplished by treating the adrenal failure as it is treated in Addison's disease.<sup>1</sup>

This is a report of four cases of severe pituitary failures of a non-Simmond's type, similar clinically to what has been termed "panhypopituitarism" by Albright and described as "Simmond's disease" by Williams and Wettenberger. Peculiar crises, similar to those which occur in Addison's disease, characterized by stupor, fever, weakness, vomiting, and hypoglycemia, were observed in one case.

**CASE 1:** A 44-year-old male. The onset of his illness began at age 39 years with a feeling of being "below par" and particularly frequent colds and weakness. In recent months he experienced increasing weakness and fatigue, both physical and mental. He tended to be excessively sleepy much of the time and lately dizziness appeared, and this at times made walking difficult. Two weeks prior to admission to the clinic he had fainted on the street and had fallen. Several times since this accident he had had to use a support to keep from falling.

The history revealed incomplete sexual maturity, essentially negative libido and potency; shaving was required once or twice a week; sparse facial hair and absence of axillary and pubic hair.

The height was 65 inches, weight, 163 pounds. He was rather pale with a very placid expression and with a suggestion of edema. Blood pressure was 90 systolic and 70 diastolic. The testes were small. The genitalia were developed to a size normal for early adolescence. The prostate was about one-half normal size.

The more important laboratory tests showed depression of the sella floor and erosion of the posterior clinoids. Visual fields and findings normal. Kepler index, 12.8 (normal above 25.0). The sugar tolerance test was normal and the insulin tolerance test was positive. The total protein was in the lower limits of the normal range. The gonadotropic hormone assays were nonmeasurable and the urinary androgens were 2.0 mg. and 0.7 mg. per 24 hours (normal, 7 to 15 mg.). B.M.R., minus 7 per cent.

The diagnosis was a calcified tumor within the sella turcica. The pituitary activity was of a very low grade and had been producing very little gonadotropic factor since before puberty. There was little evidence of hypothyroidism. The low value of urinary ketosteroids could not be accounted for by the testicular hypoplasia; the positive Kepler test supported the diagnosis of decreased activity of the adrenal cortex.

Treatment consisted of 5 mg. of *desoxycorticosterone acetate* in oil intramuscularly daily, 6 Gm. (90 gr.) of *salt* (enteric coated 1-Gm. tablets) each day, and a *high carbohydrate diet* and *intermediate feedings*.

After three injections the patient's strength increased and the dizziness disappeared. The blood pressure had risen to 126 systolic and 80 diastolic. The dosage of salt was then increased to 10 Gm. (150 gr.) daily and the desoxycorticosterone acetate reduced to 3.5 mg. three

times weekly. In addition, he was given 25 mg. of *testosterone propionate* three times weekly to favor protein retention and muscle development as well as advance genital growth and sexual maturity. After 24 days of this therapeutic régime, the following therapy was substituted: 4 pellets of 75 mg. each of desoxycorticosterone acetate were implanted subcutaneously; the dose of salt was reduced to 5.0 Gm. (75 gr.) daily, and 30 mg. per day of *methyl testosterone* was given in place of the injections of testosterone propionate. The patient was symptom free.

**CASE 2:** A white woman, age 56, gave a corresponding type of history. The diagnosis was a pituitary cyst. She lost both axillary and pubic hair and developed amenorrhea at age 36 years, following a series of pregnancies complicated by uncontrollable hyperemesis gravidarum. She complained of headache and at one time had been stuporous and blind for three days. At age 55 she had an acute illness which was similar to her initial attacks and has had recurrent attacks during the past year. A recent attack was also associated with diarrhea, projectile vomiting, stupor, hypotension, weakness, and subnormal temperature (95.6° F.). During the attack her temperature rose to 105° F. Laboratory data obtained at this time showed a blood chloride level as low as 350 mg. per cent and the blood sugar was as low as 31 mg. per cent. She responded to intravenous saline and glucose and blood transfusion. Her B.M.R. was minus 37 per cent and since that time she had taken *dessicated thyroid*, 1 gr. daily, with little relief.

When examined at age 56 years she had the appearance of a pale, tired-looking woman. The skin had a yellowish tint and her face had a puffy appearance, decidedly suggestive of myxedema. Her height was 66 inches; her weight, 117 pounds; temperature, 96.8° F.; pulse, 96; blood pressure, 115 systolic and 60 diastolic. Pubic and axillary hair were negligible. The thyroid was not palpable. The heart sounds were rather distant. The skin of the body was not characteristic of myxedema. The breasts and genitalia were atrophied. The muscles generally lacked tone.

The x-ray of the sella showed a rather marked intrasellar calcification. Adrenal cortical insufficiency was indicated by the low Kepler index, abnormal insulin tolerance, and absence of urinary androgens.

The last acute attack was characterized by increasing stupor for three days, mild headache,

and emesis; temperature, 103.1° F.; pulse, 110; blood pressure, 110 systolic and 40 diastolic. The blood chlorides were somewhat below normal, 450 mg. per cent; blood sodium was consistent with that found in Addison's disease, 308 mg. per cent. The blood potassium was within normal limits at 17.7 mg. per cent. The white count was 6,250 per cu. mm., and there was an absence of findings suggesting an inflammatory process. She was administered 10 to 20 cc. per day of *adrenal extract*. *Intravenous glucose in saline* was given.

Following control of the acute attack by the above therapy and feeding of **2100 calories by intranasal tube** and 30 Gm. of *amino acids* by mouth, she was prescribed a diet containing 300 Gm. of carbohydrates per day. Extra feedings between meals were given. The therapy was *sodium chloride*, 4 Gm. daily, and 2 mg. of *desoxycorticosterone acetate* intramuscularly daily. *Thyroid*, 0.065 Gm. (1 gr.), was continued for about one month. Her blood pressure had risen to 130 systolic and 88 diastolic, and her therapy was changed and four 75 mg. desoxycorticosterone acetate pellets were implanted subcutaneously. Her improvement was striking, but was not further improved by the oral administration of extra adrenal extract (Cortalex), one tablet three times a day.

Therapy is being maintained by implantation of desoxycorticosterone pellets, sodium chloride and thyroid as previously administered and 4 cc. of adrenal extra per day.

**CASE 3:** A male, age 39, had been complaining of anorexia and weakness for one month. Weakness, marked fatigue, anorexia with abdominal distress persisted, and 11 pounds weight loss occurred in one month.

The patient was 65.5 inches tall, span 69 inches, and weight 179 pounds. The secondary sex characteristics were deficient. The penis was less than the average size and the testes were small. The prostate was less than normal in size. The x-ray of the sella showed enlargement with elevation and erosion of the posterior clinoids. Bitemporal hemianopsia for form and color; fundi; temporal pallor of disc, Kepler index 1.4 (normal above 25.0), Gonadotropic assay, none measurable. Urinary androgens, 2.6 mg./24 hours (7 to 15). B.M.R., -15 per cent.

**Treatment:** *X-ray therapy* to the pituitary gland was administered daily for two weeks. Each treatment consisted of 200 r to three portals. *Thyroid*, 0.065 Gm. (1 gr.), daily; *testosterone propionate*, 25 mg., three times weekly by injection, and 6 to 9 Gm. (90 to 135

gr.) enteric coated **salt tablets** daily. Moderate improvement was obtained with this therapy, libido increased, and strength was somewhat better. **Desoxycorticosterone acetate** in 5-mg. doses three times weekly was added, and his general vigor and strength were much improved. Testosterone propionate was changed to **methyl testosterone**, 30 mg., daily by mouth. The patient continued to improve and later resumed his normal occupation.

CASE 4: Another case of pituitary neoplasm and the therapeutic management was essentially the same.

**Summary**—Four cases are presented showing evidence of organic pituitary lesions. In each there are symptoms and laboratory evidence to indicate the presence of adrenal cortical deficiency.

Amino acid tolerance and plasma protein levels (Tiselius) are similar to those observed in cases of Addison's disease, but differ somewhat in the height of the globulin fraction.

Response to treatment with desoxycorticosterone was good in each case. Adrenal extract, testis hormone, and thyroid were used as adjuncts to therapy. The results of treatment were better than we have been able to secure with other forms of therapy in similar cases.

#### **Treatment of Addison's Disease—**

Pellets of desoxycorticosterone do not constitute complete replacement treatment of Addison's disease. The result obtained is a maintenance of a balance of the metabolism of salt and water, which in turn produces an elevation of blood pressure. These effects are followed by increases in appetite, strength, and weight. Carbohydrate metabolism is unaffected; therefore, the hypoglycemia must be controlled by adequate carbohydrate intake. Pigmentation is uninfluenced and the patient's low resistance to infections remains. These latter failures of desoxycorticosterone therapy are in a measure offset by the convenience, to the patients, of this form of therapy as op-

posed to daily or less frequent hypodermic administration.

This<sup>2</sup> is a report of eight cases of Addison's disease who received pellet treatment over a sufficient period of time to evaluate the results of pellet implantation of **desoxycorticosterone** in Addison's disease.

The dosage of the various implantations varied as follows: 608 mg., 626 mg., 600 mg., 752 mg., 733.4 mg., 764.2 mg., 603 mg., 496 mg., 757 mg. A beneficial response to therapy was manifested by gain in weight, rise of systolic and diastolic pressure. All patients received **sodium chloride**, usually 3 Gm. (45 gr.) daily and an **adequate carbohydrate diet**.

The pellets become absorbed and a period of time occurs when the total daily absorption from the pellet is inadequate, and the patient's systolic pressure will begin to fall. At this period the daily injection of desoxycorticosterone is resumed at a dosage level selected for the individual.

If, during the period of maintenance or standardization therapy, the Addison patient contracts an inflammatory or febrile condition or requires operation, then it was found advisable and probably necessary to give additional therapy, namely, **desoxycorticosterone acetate** by hypodermic. A 37-year-old factory worker, for example, was maintained in good condition for a period of six months following the implantation of 630 mg. of desoxycorticosterone acetate. He developed a fever of undetermined etiology, which continued for six weeks. It was necessary during this period to resume his former dosage of desoxycorticosterone—2.5 mg. daily. This dosage was gradually reduced after six weeks until at the end of ten months after implantation therapy his total weekly dosage of



desoxycorticosterone acetate is 10 mg. by injection.

**Summary**—Eight patients with Addison's disease have been treated successfully with implantation of pellets of desoxycorticosterone acetate. Before implantation of pellets, careful stabilization by injections of desoxycorticosterone acetate was carried out. This permitted an accurate calculation of the number of pellets required. None of the patients suffered the results of overdosage of pellets such as generalized edema with heart failure, headache, or hypertension. Perhaps conservatism has led to using one less pellet in a few cases, which therefore resulted in an early return to added injections of desoxycorticosterone acetate. The removal of remaining pellets at some given time, such as a year following implantation, with reimplantation of a fresh supply would alleviate a period of restabilization. This was carried out in one case. This would apply only to patients without complications in whom the requirement of pellets most likely would remain the same.

The success of pellet therapy is substantiated by Bartels' experience in successfully carrying patients through illnesses and even surgery. All the patients managed by pellets are carrying out their usual occupation.

**Meningococcal Adrenal Syndromes and Lesions**—The capillaries and perivascular tissues of the brain and cord can be invaded in certain fulminating and acute meningococcal infections according to Banks and McCartney,<sup>3</sup> and in this form of meningococcal infection encephalomyelitis may be present concurrently with bilateral adrenal hemorrhage. They state that this combination is probably not uncommon in severe cases during an epidemic. They observed it in three out of nine cases reported in 1942.

This paper submits evidence that the meningococcal adrenal syndrome (fulminating septicemia, massive purpura, and bilateral adrenal hemorrhage) is not a single entity but a composite one. Gross adrenal hemorrhage is easily recognized at autopsy, but the encephalitic lesion is just as easily overlooked.

The meningococcal adrenal syndrome can be differentiated into a pure adrenal syndrome, with the main organic lesion confined to the adrenals and a mixed or encephalitic adrenal syndrome in which significant lesions are present in both the brain and the adrenals. The former does not seem to be invariably fatal, because modern treatment has developed a "recovery adrenal syndrome."

The adrenal pathology in the encephalitic adrenal syndrome varies; besides hemorrhage there may occur thrombotic necrosis, edema, focal areas of inflammatory adrenalitis.

The pure adrenal syndrome (Waterhouse-Friderichsen) occurs not only from meningococcus, but the pneumococcus, staphylococcus, hemolytic streptococcus, Pfeiffer's bacillus, and *Neisseria flava* II are among the organisms held responsible.

Two distinctive clinicopathological syndromes with involvement of the adrenals are thus differentiated. The first is here described as the pure adrenal syndrome and the second as the mixed or encephalitic adrenal syndrome. It is realized that in some cases the differentiation may not be completely sharp. Both syndromes include the signs and symptoms of collapse due to acute adrenal failure. The mixed syndrome includes, in addition, such cerebral signs as deep coma and rapid stertorous breathing.

The main features common to both syndromes comprise: Sudden onset, fulminating septicemia, petechial and massive purpuric rash, cyanosis, grayish



pallor, vomiting, often diarrhea, dehydration, and acidosis if not too rapidly fatal, rapid, thready, or imperceptible pulse, very low blood pressure, general muscular flaccidity, with or without slight neck rigidity. Exceptionally, instead of a fulminating there may be an acute course with adrenal signs supervening 24 hours or more after onset. Meningitis may be present in both syndromes or absent in the most rapidly fulminating cases. Cyanosis, in its most gross form resembling postmortem lividity, is perhaps more characteristic of the pure adrenal syndrome but at least a dusky cyanosis is common to both types.

The main differentiating clinical features between the two syndromes are: (1) The state of consciousness, and (2) the type of breathing. Mental clarity and normal or "air-hunger" type of breathing with restlessness in the pure adrenal syndrome, contrasts with coma and rapid, stertorous, or irregular terminal breathing in the mixed syndrome. Other distinctive clinical signs which may be present in the mixed syndrome are convulsions, contracted pupils, incontinence of urine and feces, papilloedema of more than one diopter, and extensor plantar reflex. In the recovered cases an assessment must be made purely on a clinical, bacteriological, and biochemical basis. The most significant factors are fulminating septicemia with recovery of the organism from blood or spinal fluid, massive purpura, and very low blood pressure. Biochemical findings are bound to be limited to a few isolated observations in such an acute disease. There is no time, for example, for an exact determination of the sodium and potassium balance. Hypoglycemia, if present, is rapidly affected by the glucose used in treatment. Ketosis, diminished alkali reserve, and raised blood urea are likely to be present at the most critical stage of

the illness, and a low serum sodium may or may not be found. No case suggestive of recovery from the mixed syndrome has been met with.

Treatment must be immediate and vigorous from the moment the diagnosis is suspected. An immediate intravenous injection of *sulfathiazole* or *sulfapyridine* should be given, followed by high dosage of the drug either by mouth or by injection if there is much vomiting or deep coma. For the acute adrenal crisis the treatment comprises repeated *intravenous glucose and saline*; *intravenous cortical extract* and *intramuscular desoxycorticosterone acetate* or *cortical extract* alternately every four or six hours until the blood pressure improves; *warmth* and *stimulants* as for shock. With early diagnosis and treatment of these lines, failure is not inevitable and there may even be a reasonable prospect of success.

The authors describe a case of the pure adrenal syndrome in a female aged 34 years. The onset of the illness was sudden with shivering, vomiting, and diarrhea for eight to ten hours and a purpuric rash. The patient was conscious and mentally alert on admission, but was restless and shocked. Petechial and general purpuric eruption was present. The heart sounds were faint and the radial pulse was imperceptible. The blood pressure: 70/40 mm. of mercury, no meningococcal symptoms, spinal fluid clear and under very low pressure contained 25 cells (mononuclears) per mm. Blood culture: Meningococcus, Group I. She was administered 10 cc. Eucortone (*adrenal cortical extract*) and *normal saline* by intravenous drip, *sulfathiazole*, 2 Gm. (30 gr.) intravenous and 2 Gm. (30 gr.) by mouth two hours later.

Five hours after admission she vomited black blood and died five minutes

later. Consciousness and ability to converse were maintained to the end.

The autopsy revealed numerous petechia in the stomach, intestinal wall, pericardium, and pleura. The adrenals were plum colored, the structure of medulla and cortex obliterated. Sections of the adrenal showed peripheral hemorrhage, bulk of medulla and cortex necrosed, large vessels of the medullary portion were thrombosed. Necrosed cells, separated by hemorrhage. The meninges and the choroid plexus were congested. Sections of the cerebral cortex, mid-brain, and pons: Congestion and edema, with an occasional minute hemorrhage.

The second was a female aged 14 years. Sudden onset with swelling of legs and arms, headache, and vomiting; purpuric rash, slight sore throat; conscious but occasional mild delirium.

On admission, massive purpuric hemorrhages, 2 to 6 cm. wide, covering the face, limbs, buccal mucous membrane, and conjunctiva; rigid neck and positive Kernig's sign. Reflexes normal, temperature 101° F., pulse 120 (very poor volume). Spinal fluid: Pressure slightly increased; clear, few polymorphonuclears, numerous meningococci. Conscious to the end. Death in 24 hours. Therapy: *Sulfapyridine*. Autopsy: Brain and cord; purulent meningitis edema; adrenals—massive hemorrhages; sections—hemorrhage, necrosis, thrombosis of vessels.

The third case was a male aged 19 years who died 36 hours after onset of illness. Meningococcus II in blood culture. Spinal fluid clear, under pressure one white cell and numerous red; meningococcus from culture. Autopsy: Adrenal—intensely hemorrhagic: section—hemorrhage, necrosis, thrombosis.

The fourth case was a female aged three years. Sudden onset at 6 A. M. and died at 10 P. M. within three minutes of

admission, at which time she was pulseless and moribund but was conscious and rational on her way to the hospital. Adrenals—plum colored; section—severe hemorrhage involving almost all of the cortex and medulla; necrosis of cortical cells.

Three cases are reported in which the presence of adrenal lesion and the pure adrenal syndrome is assumed on the basis of the signs and symptoms.

Case 1 is a female aged 7½ years. Sudden onset with vomiting, slight diarrhea, increasing restlessness and drowsiness; headache occurred about the fourth hour later, and a petechial rash seven hours later. She was admitted 9½ hours after the onset of her illness in an acutely ill state, with slight cyanosis, neck rigidity, faintly positive Kernig, temperature 103.8° F., respiration 38 per minute, pulse just perceptible, blood pressure 86/50 mm. of Hg., one hour later 64/40. Spinal fluid clear; pressure, normal, 92 cells per cc. (polys 80 per cent), meningococci (Group I on culture). Treatment: 1 Gm. (15 gr.) *sulfathiazole sodium* intravenously, then 1 Gm. (15 gr.) four hourly for 12 hours by mouth; glucose drinks, 10 per cent *glucose in normal saline* rectally by continuous drip; 4 cc. *Eucortone* intramuscularly. Approximately four hours later her condition was worse, radial pulse just perceptible, rate at apex 176 per minute, color poor, rash increasing, very restless but conscious. Loose stools, blood pressure 56/25; *Eucortone*, 2 cc., and 10 Gm. (150 gr.) glucose given intravenously produced prompt improvement in pulse and color, and blood pressure rose to 68/40. Eight hours later relapsed and she was again given 2 cc. of *Eucortone* and 10 Gm. (150 gr.) glucose intravenously and 550 cc. of normal saline intraperitoneally. Blood pressure improved—70/40; *sulfathiazole*,

0.75 Gm. (12 gr.) four hourly by mouth and Eucortone, 5 cc. intramuscularly, alternating four hourly with *desoxycorticosterone acetate* (5 mg. in 1 cc. oil), 10 Gm. (130 gr.) of glucose intravenously were given four hours after the previous one. Blood pressure 80/60, much quieter and taking fluids, speaking a few words. The spinal fluid was now turbid and under pressure, cells 1150 per cc. (polys 80 per cent), no organisms, sulfathiazole content (free) 2.7 mg. per 100 cc. Very slight muscular rigidity.

**Summary and Conclusions**—Eleven cases of meningococcal adrenal disease are described, of which eight were fatal and proved at autopsy, and three recovered, the diagnosis being presumed. Meningococci were isolated from six of the fatal cases and from two of the recoveries.

In four of the fatal cases no significant organic lesion other than meningitis was found in the brain or cord, but in the remaining four there was evidence of diffuse or focal encephalomyelitis (capillary thrombosis, hemorrhages, and perivascular cuffing) or of very gross edema.

Clinically, the former group and also the three recovered cases showed relatively clear consciousness maintained almost to the end, and normal, rapid, noiseless or acidotic breathing, while those with a cerebral lesion were deeply comatose and had rapid stertorous breathing.

It is suggested that in meningococcal (and possibly in other infective) disease involving the adrenals there are two distinct clinicopathological syndromes: (1) Pure adrenal, and (2) mixed or encephalitic adrenal.

Prompt diagnosis and immediate sulfonamide treatment of the infection with vigorous replacement therapy for the adrenal crisis may lead to recovery, at

The pathological lesions found in the adrenals comprised not only pure hemorrhage but also thrombotic necrosis with hemorrhage, gross edema, and focal inflammatory adrenalitis.

**Pheochromocytoma of the Adrenal Gland**—The sympathetic formative cells (sympathagonia) of the adrenal medulla differentiate into two systems, the ganglion cells and the pheochromocyte. Tumors of the medulla arise from the same cells but only the pheochromocyte tumor is a hormone-producing tumor.

The pheochromocyte tumor of the adrenal medulla,<sup>4</sup> designated pheochromocytoma, is also known as chromaffinoma, paraganglioma. The tumor is found not only in the adrenal medulla but may arise wherever chromaffin tissue is present (retroperitoneal tissue, carotid body, along the abdominal aorta, the organ of Zuckerkandl, sacrococcygeal region). The tumor is usually benign, of variable size, millimeters to centimeters.

The symptom complex is produced by the discharge into the general circulation of adrenalin or an adrenalinlike (pressor) substance. The pressor substance, which produces the exaggerated response of the body to the hormone can be demonstrated in the blood and if the tumor is adrenal medulla and of sufficient size, the presence of the tumor can be demonstrated by perirenal insufflation.

The symptomatology of pheochromocytoma is typical but may vary in severity. The typical attack consists of a marked pounding headache, nausea, dyspnea, orthopnea, palpitation, blanching of the peripheral portions of the body, paresthesias, abdominal cramps, vomiting, precordial throbbing, and marked weakness. The duration of the attack may vary from a few minutes to

tient may be in shock. The termination of the attack is accompanied by flushing of the blanched areas, marked perspiration, and weakness. However, death may occur during the attack from shock, pulmonary edema, left heart failure, coronary disease, or with cerebral manifestations. Surgery is the required treatment for pheochromocytoma and if this is not pursued the pressor attacks produce arteriolar sclerosis and hypertension.

The attacks may occur spontaneously or they may be induced by emotional upset, fear, anger, slight trauma, physical exertion, change in posture, from reclining to upright position, lying on the side of the tumor or massaging the tumor site, the administration of histamine or adrenalin or the immersion of the extremities in cold water. A trivial operation may induce a fatal attack.

The hypertensive attacks are characterized by systolic pressures up to 300 mm. and diastolic pressure of over 100 mm. of mercury. The pulse is markedly thin and unpalpable. Marked peripheral vasoconstriction occurs and this may be confirmed in the fundus oculi and the capillary beds of the fingers. The pulsation of the carotid artery may be barely palpable because of the severe constriction. The differential spread in pressure reading between the brachial artery and the digital artery is characteristic of the hypertension produced by adrenalin.

The skin temperature is lowered and rectal temperature may be elevated.

The prolonged vasoconstriction produces the state of shock, or the state of hock which usually follows removal of the tumors is due to relaxation of the blood vessels, the low blood pressure and resultant anemia of the vital centers.

The sugar tolerance tests usually show diabetic type of curve. The blood volume measurements show a decrease. Perfusion tests of blood obtained at the

height of an attack have shown positive response for pressure substance in animals in some cases. The urine is usually decreased in volume, contains albumin, red blood cells and casts, and glycosuria may be present.

X-ray studies are helpful in diagnosis. When a large pheochromocytoma is present, pyelography may show a compression of the upper pole of the kidney. A small tumor may not press upon the kidney; perirenal insufflation will demonstrate and localize the small pheochromocytoma. The electrocardiogram may show abnormalities referable to the left ventricular preponderance.

The administration of sedative, *ergotamine* or *nitroglycerine*, may occasionally control the attacks.

Hypertension, hyperthyroidism, and coronary occlusion must be differentiated from pheochromocytoma.

The therapy advised for pheochromocytoma is *surgical removal of the tumor* which usually involves the removal of the adrenal gland. It is therefore required that preparations be made to treat the patient for acute adrenal cortical insufficiency before and after operation as well as the hypotension which usually follows the removal of the tumor.

This report concerns the clinical findings in four cases of pheochromocytoma.

CASE 1: A female, single, age 26, first complained at age 17 years of mild fatigue, throbbing headaches, and sweating. A diagnosis of hyperthyroidism was made and subtotal thyroidectomy performed. No improvement occurred, in fact the symptoms increased in severity, and two years later she first observed vasoconstriction phenomena in the terminal phalanx of the right index finger. The vasoconstriction phenomena gradually extended to all digits, the distal portion of the extremities, and the tip of the nose.

Eventually attacks of nausea and intense generalized headache occurred, and these were followed by precordial throbbing and a feeling of exaggerated pulsations of the vessels of the neck.

Dyspnea and on occasions orthopnea appeared. The vasoconstrictor changes occurred in her fingers and other areas. The symptoms abated in about five minutes and terminated with profuse perspiration and weakness. The attacks had been occurring weekly; the attacks increased in severity and frequency until they were occurring almost every half hour.

The patient was a thin, underdeveloped, young white female, who sweated profusely and appeared chronically ill. Other noteworthy physical findings were a rough systolic murmur at the base, the aortic second sound was louder than the pulmonary, and a blood pressure of 230/180. The range of blood pressure was from 140/100 to 280/200. (Elevated B.M.R.'s plus 69, 39 and 27 per cent.) Sinus tachycardia, rate 115 per minute. Adrenalin sensitivity, 2 minims of 1:1000 adrenalin produces an unusually high rise in systolic pressure. Exercise induced an attack. Pressor substance was demonstrated in the blood. The adrenal tumor was demonstrated by x-ray (retrograde pyelogram and perirenal insufflation) to be on the left side.

The tumor was removed and demonstrated to be a pheochromocytoma.

CASE 2: A 23-year-old female with an onset of acute symptoms at age 20½ years. The attacks consisted of severe frontal and occipital headaches, dizziness, weakness, epigastric, back, and neck pain and nonprojectile vomiting. Six months later the attacks became more frequent and were associated with a choking sensation, dyspnea, orthopnea, palpitation, blanching of extremities and face, and sweating. The attacks then occurred at monthly intervals and usually at the end of the menses. At age 22 years, after five months' hospitalization, the left adrenal was explored for a pheochromocytoma. The left adrenal gland was normal. The attacks continued with the typical attacks being characterized by sudden onset of palpitation, pounding headache, blanching of the face and extremities, abdominal cramps, nausea and vomiting, and finally profuse sweating. The blood pressure would rise from 140/100 mm. to 310/180 mm. of mercury.

Originally the attacks, which lasted from 15 minutes to an hour or more, were now lasting beyond eight to 12 hours, and eventually were from 24 to 36 hours and followed by shock for a period of a few hours.

Attacks could be induced during fear, anger, excitement, sexual intercourse, a change from prone to sitting position, hyperventilation.

Perirenal insufflation and x-ray revealed a mass on the right kidney and at operation a tumor of the right adrenal gland was found and removed. Palpation of the tumor caused a rapid high elevation of systolic pressure. This reaction ceased when the blood supply to the adrenal was completely ligated and severed.

Preoperatively, the patient received *desoxycorticosterone acetate* and *saline*, during the operation *adrenal cortical extract* and *adrenalin* by hypo, and adrenalin in oil during and after the operation. Postoperatively, the blood pressure ranged between 70/50 mm. of mercury and 90/65 mm. of mercury as compared to the 120 mm. at the onset of operation, 220 mm. of mercury during the removal of the tumor.

Recovery of the patient was uneventful, she was free from symptoms, and she had gained 20 pounds in three months.

CASE 3: An orange-sized tumor, lying above the kidney, could be palpated in the left flank. The blood pressure of this 41-year-old male was 130/90 mm. of mercury. His symptoms were typical and were induced by pressure or irritation of the left side of the abdomen. Intravenous pyelography demonstrated an adrenal mass displacing the left kidney downwards. A pheochromocytoma was removed with the kidney. The mass was adherent to the kidney. This state also existed in Case 1 and was similarly treated.

CASE 4: A niece of Case 1, 17 years old; family history was of unusual interest. Her mother and sister had had thyroidectomies, and an older sister had had a thyroidectomy and died at age 28 years. The latter was supposed to have had a rare disturbance of the sympathetic system (according to the hospital record) and her symptoms were strikingly suggestive of those of Case 1.

The patient's symptoms started with a sudden pounding, splitting headache, agitation, palpitation, and pallor and tingling of the fingertips. The attacks lasted 15 minutes and one attack was induced by hyperventilation. A slight constant headache was present.

The patient was a well-nourished, moderately thin girl. The thyroid gland was moderately and diffusely enlarged. Heart—precordial systolic murmur and heart sounds. Blood pressure, 158/92 mm. of mercury and varied during her study from 132/90 to 180/100; during attacks the blood pressure rose to 210/140 to 234/100. An attack could be induced by carotid sinus pressure. The urine showed a faint trace of albumin.

A left perirenal insufflation showed a tumor mass in the region of the left adrenal. This was confirmed and removed and one-half of the left adrenal was left *in situ* at operation. Diagnosis: Pheochromocytoma of the left adrenal gland.

Immediately after operation the blood pressure fell to 70 mm. of mercury and the pulse rate was 100. The administration of 5 mg. of *desoxycorticosterone acetate* for two doses, 0.25 cc. of *adrenalin* and *transfusions* controlled her condition and thereafter she steadily improved.

A long period of follow-up in all these cases reveals that the patients are in excellent health and they have experienced no further attacks.

The diagnosis of pheochromocytoma is based on: (a) The typical symptomatology during an attack (spontaneous or induced); (b) the typical pressor response mechanisms; (c) the demonstration of pressor substance in the blood of a patient during the height of an attack; (d) the demonstration of the tumor by perirenal insufflation.

The pheochromocytoma causes a surgically remediable form of paroxysmal hypertension.

### Adrenal Carcinoma

**Bilateral Carcinoma of the Adrenal Cortex with Metastasis to the Iliac Bone**—Cleveland and Knox<sup>5</sup> report a male, aged 57 years, whose chief complaint was pain in the region of the right hip. The pain at times radiated along the right sciatic nerve. There was loss of weight; eventually the sciatic pain become constant. There was localized tenderness, "feeling like a boil," in the right inguinal region.

A palpable tumor, involving the right iliac crest and the anterior superior, was present. X-ray studies defined a destructive process involving the right ileum.

The physical appearance and the clinical findings in the patient presented no evidence of Cushing syndrome. The

blood pressure was systolic 120 and diastolic 74 mm. of mercury.

The patient was operated for a section of the tumor. The patient went into shock two hours after this simple operation and never regained consciousness or rallied from shock.

The chief postmortem finding, besides the local bone pathology, was the practical destruction of both adrenal glands by carcinoma; both the cortex and medulla were replaced by the malignant process.

Sections of the pituitary revealed normal cells in both the anterior and posterior lobes.

### Nonhormonal Adrenal Adenoma

The case report<sup>6</sup> concerns a 37-year-old female who complained of abdominal pain and a mass in the abdomen. During the past two years she had lost 107 pounds. Her previous weight had been 240 pounds.

There were no signs of virilism. Recently the menses had been irregular and the blood pressure was 130/80. A large, firm, solid mass was palpable and rooted to the right posterior abdominal wall.

Abdominal section was performed and a large, irregular, spherical mass weighing 4200 Gm. was removed from the right upper quadrant. The right kidney was displaced downward for about three inches and was rotated on its longitudinal axis; the liver was displaced forward and to the left.

The histological study of the tumor revealed it to be an adrenal adenoma.

**Comment**—The foregoing two case reports show that extensive pathology may occur in the adrenal gland or glands without an endocrine disorder being present. In the case of Cleveland and Knox<sup>5</sup> it is of interest to note the presence of extensive destruction of the adrenal cortex without Addison's disease occurring. This patient, however, could



stand extremely little operative procedure without shock occurring.

**Adrenal Cortex in Systemic Disease** — Sarason<sup>7</sup> studied the adrenal glands in 110 patients with systemic disease and found that cortical enlargement associated with depletion of lipid or reversal of lipid was found associated with inflammatory disease, cachexia, pemphigus, and protracted emesis. He believes his study emphasizes that the above changes in the adrenal gland are reflections of the metabolic changes associated with certain systemic diseases and are not the direct effect of the latter. The morphological changes in the cortex take on physiologic significance, lending themselves to functional interpretations.

## HYPERTENSION

**Endocrine Aspects** — The authors<sup>8</sup> state that high blood pressure is also a concomitant of various endocrine disorders.

Hypertension is observed in myxedema and in the early stage of hyperthyroidism and in diabetes mellitus and from the thirty-fifth year on the incidence of hypertension increases.

Hypertension is common in both the female and male climacteric period.

The relationship of pituitary disease to hypertension, except in the instance of Cushing syndrome, is less well defined.

Disorders of the adrenal cortex and medulla play a large rôle in hypertension. The pheochrome tumors of the medulla are associated with paroxysmal hypertension. In adenoma or carcinoma of the adrenal cortex, also capable of producing the Cushing syndrome, hypertension is a common finding.

The adrenal cortex plays a leading rôle in regulating salt and water metabolism, and overfunctional adrenal cortical states lead to salt and water reten-

tion. A similar state occurs in hypothyroidism. The hypertension of hyperthyroidism appears to be the result of an abnormal sensitivity of the sympathetic system.

The common feature of obesity and the accompanying state of water retention links into one group, the hypertensive cases of diabetes, climacteric, and the various pituitary disorders.

Investigation of the salt and water metabolism of 100 unselected cases of hypertension revealed that 71 per cent retained water and 83 per cent retained salt. These findings, which were obtained by a salt tolerance test, indicated that salt and water retention must be corrected.

The therapy consisted of *ammonium chloride*, 0.5 Gm. (7.5 gr.) (enteric coated tablet) three times a day. After five days this therapy was replaced by *potassium acetate* in order to increase the elimination of the chlorides. The addition of sedation, in the form of *atropine sulfate* ( $\frac{1}{300}$  to  $\frac{1}{150}$  gr.) and *phenobarbital* (0.25 to 0.5 gr.) twice a day during the initial period of therapy produces a favorable response in reducing the blood pressure. In hypothyroidism and the sex hormone deficiency case the respective hormones are administered. Posterior pituitary extract injections produced favorable response in provoking diuresis; a temporary period of antidiuresis precedes the diuretic effect of posterior pituitary extract.

The results of these therapeutic efforts were striking. The 100 patients lost an average of 25 pounds with a maximum of 73 pounds in one case. The six underweight patients, included in the series, gained a total of 34 pounds, an average of 5.5 pounds. The mean blood pressure of the whole group after treatment was calculated at 142/85 mm. Hg. as compared with 179/103 mm. Hg. be-



fore the treatment. Therapy failed in three cases, including one patient observed for eight years, who had not heeded earlier advice to seek surgical relief. The two other cases were treated for only two and four months, respectively, and their cooperation was questionable. The time of treatment and observation for the whole group averaged 13 months.

**Summary**—The relationship between abnormal blood pressure and varied endocrinopathies is reviewed. Disturbances of salt and water metabolism are demonstrable in the diseases reviewed and show a coincidence of hypotension and a loss of salt and water on the one hand and of hypertension and retention of salt and water on the other.

The results of study of a series of 100 hypertensive patients are presented. The data demonstrate the association of salt and water retention and hypertension in the endocrine patients. Increased values for red-blood-cell chlorides were also obtained.

Treatment of these patients with dietary and medicinal methods aimed at relief of the retention phenomena produced a considerable drop of blood pressure which was maintained during a prolonged period of observation. The clinical results were improved by the addition of sedation in the ambulatory patient and by appropriate endocrine therapy.

### ESTRONE SULFATE (CONJUGATED ESTROGENS-EQUINE)

Four papers reporting the results obtained by the administration of estrone sulfate, a natural estrogen, are presented.

Estrone sulfate, a naturally occurring estrogen, is found in the urine of pregnant mares. It is a water-soluble substance and is several times more potent

than free estrone when orally administered to spayed rats.

Freed, Eisin and Greenhill<sup>19</sup> administered *estrone sulfate* in three dosage levels: 1.25 mg., 0.81 mg., and 0.4 mg. (tablets), three times a day to a group of patients who complained of moderate or severe menopausal symptoms, at least two hot flashes daily, nervousness, and dizziness. The patients (60 cases) received the highest dosage level for two weeks. The results were complete relief in 43 per cent and satisfactory relief in 43 per cent, and 14 per cent obtained slight or no relief. The patients were then administered estrone sulfate in the next lower dosage level and after two or three weeks the results evaluated. The findings were as follows: 47 cases 0.81 mg. of estrone sulfate three times a day: complete relief, 38 per cent; satisfactory relief, 42 per cent; slight or no relief, 20 per cent. Forty-five cases who received 0.40 mg. of estrone sulfate three times a day obtained complete relief in 26 per cent, satisfactory relief in 57 per cent, and slight or no relief in 17 per cent.

The side effects of estrone sulfate were almost negligible (one case of nausea) when the daily total dose was 1.20 mg.; 2.50 mg. daily produced nausea in two patients, and two complained of dizziness, and 3.75 mg. daily produced nausea in five patients and dizziness in four patients.

Uterine bleeding developed at all dosage levels; it was most frequently observed (five cases) in the lowest dosage level group; next in frequency in the intermediate dosage (two patients), and least (one case) at the highest dosage level.

The authors compare the results obtained with estrone sulfate and *diethylstilbestrol* (stilbestrol). They state the results obtained with 1.2 mg. of estrone sulfate daily are superior to those with

0.5 daily; 2.4 mg. daily estrone sulfate is slightly superior to 1.0 mg. daily of stilbestrol (NOTE: The statistical table used for comparison reads 0.5 mg. t.i.d. and 1.0 mg. t.i.d.).

The authors consider that the average therapeutic dose of estrone sulfate is 1.2 mg. daily. This represents 0.9 mg. of estrone; this quantity compared to 0.5 mg. of stilbestrol gives a ratio of effectiveness between the two substances of 1 to 2. In view of the higher toxicity of stilbestrol at this effective level (10 to 20 per cent), estrone sulfate is the more desirable of the two estrogenic agents; further, the patients receiving estrone sulfate experience a greater sense of well being along with the relief of the major symptoms.

Gray<sup>10</sup> studied the effect of estrone sulfate in 64 women in the menopause. The chief symptom was hot flashes. Nervousness, excitability, sleeplessness, gastrointestinal complaints, and arthralgia were observed in a varying degree in a considerable number of patients. The severity of the symptoms and vaginal atrophy were graded in the 64 patients. Symptoms: 15, 4+; 32, 3+; 13, 2+, and 2, 1+. Vaginal atrophy: 32, grade 4; 18, grade 3; 5, grade 2, and 7, grade 1. The effectiveness of estrone sulfate therapy was graded on the degree of relief of symptoms and changes in the vaginal smear.

**Dosage**—In this series 1.25 mg. of estrone sulfate was given daily for from seven to 14 days and then 1.25 mg. every other day for maintenance. Improvement in symptoms was considered complete or marked in 46 of the 64 patients studied. Eight showed moderate improvement, three manifested slight improvement. In seven cases accurate data were not obtained. Restoration of normal vaginal epithelium was considered complete in 45 cases. Fifteen patients

did not have vaginal or smear studies. The remainder showed subfollicular stage smears.

Four of the patients studied experienced bleeding during treatment. One bled after taking 1.25 mg. daily for 58 days; two bled after taking 1.25 mg. daily for seven days and 1.25 mg. every other day for 30 days; one patient had two periods of bleeding after taking a daily dose of 0.31 mg. for 15 days.

Only one patient in the 64 treated with estrone sulfate complained of nausea.

A greater sense of well being following the estrone sulfate was noted by the patients who had previously been treated with stilbestrol. Patients who had been treated with parenteral estrogen observed a better maintenance effect with oral therapy.

Glass and Rosenblum<sup>11</sup> state they deemed the continued use of stilbestrol inadvisable because of: (a) its lack of tonic properties observed in the natural estrogens; (b) frequency of withdrawal bleeding as a complication, and (c) unknown factors of toxicity, (nausea, skin eruption, other side reactions).

Their report concerns 71 menopausal patients treated with estrone sulfate for six to 10 months. Initial dosage varied from 2.5 to 3.75 mg. daily. This was gradually reduced to 1.25 daily. Maintenance was possible eventually with 1.25 mg. three to five times weekly.

In the 71 patients complete relief was obtained in 58 patients or 82 per cent, partial relief in seven patients or 10 per cent and poor results in six patients or 8 per cent. Twenty of the patients treated were cases of artificial menopause; in this group complete relief was obtained in 14 cases or 70 per cent; partial relief in three cases or 15 per cent; and negative effect in three cases or 15 per cent. In the physiological menopausal cases (51 cases) complete relief was ob-

tained in 86 per cent; partial relief in 8 per cent and negative effect in 6 per cent.

The incidence of undesirable side effects was minimal in this group: One case of abnormal bleeding and one case of nausea. Resumption of menses occurred in seven cases.

The authors conclude that these favorable results with estrone sulfate have justified discontinuing the use of diethylstilbestrol in routine therapy in the menopause. In this group of patients the sense of well being established by estrone sulfate was noted by patients previously treated with stilbestrol.

Sevringhaus and St. John<sup>12</sup> report their results in 25 women treated with estrone sulfate. Eleven cases of physiological menopause and 11 cases of surgical menopause obtained complete relief of their symptoms after the administration of estrone sulfate. The ages of the 25 women ranged from 31 to 62 years; fourth decade, five cases; fifth decade, 11 cases; sixth decade, eight cases; seventh decade, one case.

The dosage of estrone sulfate administered was 1.25 mg. one to three times daily.

They established evidence of the potency of estrone sulfate by the transformation of the vaginal smear, from the atrophic type to a 4 plus activity. Vaginal bleeding was produced in a 61-year-old female who had had no vaginal bleeding for 19 years and a second case in whom no vaginal bleeding had occurred for nine years (postopphorectomy and subtotal hysterectomy).

Clinical experience with oral administration of tablets of conjugated estrogens-equine, in doses of 1.25 mg., one to three times daily, has shown this new variety of estrogenic preparation from pregnant mare's urine to be a dependably helpful agent in giving complete relief

from the common autonomic, emotional, and mental complaints of the menopausal syndrome.

**Editor's Note** Estrone sulfate (sodium estrone sulfate) is the newest natural estrogen available for treatment of the hypoövarian state, particularly the menopausal or climacteric state. One of the difficulties in evaluating the effectiveness of estrogenic agent in the menopausal state is the reporter's conception of what group of symptoms constitutes the menopause. When a gynecologist reports of his therapeutic results, one usually finds that the patient is complaining of flashes, nervousness, restlessness, or sleeplessness. It is quite natural that he does not see the more complex or advanced menopausal patients with head pains, depressions, melancholia, palpitation, sense of choking, severe emotional instability, and those in a debilitated state and having the feeling of total inadequacy. This type of patient is probably more often seen in the endocrine clinic. In other words, there are all degrees of the menopausal state; therefore, it is quite natural that in therapeutic studies of this type we will find varying conclusions as to the therapeutic values of an estrogenic agent and as to the average and optimal dosage required.

These four clinical therapeutic studies reveal this state of affairs. Freed *et al.*<sup>9</sup> obtained optimal results with 1.25 mg. daily, and Gray<sup>10</sup> obtained similar results. These reports are from gynecological clinics. Glass and Rosenblum,<sup>11</sup> and Sevringhaus and St. John,<sup>12</sup> reporting from an endocrine and medical department, respectively, find that from 2.5 to 3.75 mg. are required to obtain effective relief in the menopausal syndrome. After a period of treatment with this higher dosage which produced a readjustment in the disturbed endocrinous balances of the menopause, then a lower

maintenance dose of 1.25 mg. is found satisfactory. That the endocrinous imbalance of the menopause is a variable and responds differently, qualitatively and quantitatively, to the numerous natural and synthetic estrogens is shown by the varied effect in the physiological and surgical menopausal cases in the report of Glass and Rosenblum.<sup>11</sup>

The reports of the study show that while estrone therapy relieves a very favorable percentage of the menopausal cases treated there have been an appreciable percentage of ineffective relief and failures. Unquestionably this is the group of true menopausal cases which require intensive parenteral natural estrogenic therapy. The reports on estrone sulfate clearly set forth the fact that the synthetic estrogenic substances do not possess the therapeutic ability to create in the treated patient "a sense of well being." This state of general improvement is only observed by the menopausal patient when she is treated with the natural estrogen.

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## GONADOTROPIC THERAPY IN GYNECOLOGY

Davis and Hellbaum<sup>13</sup> state that the lack of uniformity in the results obtained from the clinical use of gonadotropins is due first to the defects in our knowledge of the physiology of human reproduction and, secondly, the clinical problem of ovarian failure is still a crude entity, the etiology of which may or may not be known.

The patient for gonadotropic therapy is often poorly selected; therefore, the results attributed to gonadotropic therapy in many clinical reports "are subject to a wide variety of interpretations." The gonadotropins should be useful in the treatment of an ovarian failure which is

caused by a deficient anterior pituitary stimulus.

The authors cite the importance of the interrelationship of the actions of the three human gonadotropic factors: The follicle stimulating hormone (L.S.H.), the luteinizing hormone (L.H.), and luteotropin—on ovarian function. According to recent studies of ovarian physiology, luteotropin is necessary to maintain the corpora lutea and luteal tissue in an active secretory state for the production of progesterone.

This paper reviews the extensive studies concerning the use of chorionic gonadotropins in ovarian failure in the human being and the results clearly demonstrate that chorionic gonadotropin is without power to stimulate development of graafian follicles or to produce maturation and liberation of the ova in primates. The findings are that the large follicles become atretic while small follicles become hyalinized, concomitant with decreased ovarian secretion. The work of Brown, Bradbury, and Metzger is quoted, which showed that prolonged treatment with chorionic gonadotropins in women having normal menstrual cycles leads to atrophy of the endometrium.

Equine gonadotropin (P.M.S.) shows physiological activity similar to the effect of the anterior pituitary gonadotropic factor and it is obtainable in a very pure state. It is slowly metabolized in the body and is not excreted by the kidney; consequently, it remains with the blood stream at a relatively high concentration.

The authors review the results obtained with pregnant mares' serum and state: "The present status of equine gonadotropin in clinical practice is far from clear. The many conflicting reports in the literature indicate the lack of uniformity in the results obtained. There is no agreement as to the optimum dosage, the method of administration, or the time

relationship—its application to gynecologic therapy has thus far been disappointing.”

The anterior pituitary preparations are capable of stimulating the primate ovary. Results obtained with this fraction are also conflicting. “The indecisive results in the past may well be due to our failure to appreciate the quantitative relationship which exists between the various gonadotropic factors and the period of time during which the various factors are exerting their stimulative effects.”

The combination of chorionic gonadotropin and anterior pituitary extract or pregnant mares' serum has been utilized on the basis of an augmented or synergistic reaction between these two gonadotropins. The results obtained by Mazer and Ravitz with the synergy units were definite stimulation of the ovaries in 20 of the 23 patients treated. Geist, Gaines, and Salmon were of the opinion that the stimulating effect obtained with “synergy units” was no greater than that obtained with anterior pituitary extracts.

Davis and Hellbaum<sup>13</sup> state that reviews of the action of the various gonadotropins emphasize the fact that gonadotropic therapy is thoroughly unsatisfactory in our present state of knowledge and they state that changes ascribed to gonadotropic therapy are often the result of existing pituitary gonadal activity. We do not know the cause of functional bleeding so that gonadotropic therapy is illogical at the present time and that thyroid therapy is much more efficacious in many of the cases of functional bleeding in young women. Progesterone will cure a number of these cases and many women with irregular bleeding will revert to a normal menstrual pattern without therapy.

Gonadotropic therapy is not indicated in an amenorrhea due to primary ovarian

failure. The ovary in some cases may be refractory to anterior pituitary stimulation or in a state of “physiological exhaustion.” The age and the physical condition of the patient may have a marked influence on the response of the ovaries to an injected gonadotropin. The authors conclude that successful gonadotropic therapy must await the elaboration of pure gonadotropic principles from the anterior lobe of the pituitary.

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## MENSTRUAL DISORDERS

**Pitressin Tannate in Oil in Menorrhagia and Metrorrhagia** Ten patients, four with menorrhagia and six with metrorrhagia of the premenopausal and menopausal type, were administered one or two doses of 1 cc. of *pitressin tannate in oil*. Without exception the excessive vaginal bleeding ceased within six to 72 hours.

One case of menometrorrhagia, a young girl, had bled for two months and in another case the bleeding was of 28 days' duration. In each case two injections of pitressin tannate in oil were sufficient to control the bleeding.

To prevent a recurrence of the menorrhagia at the next menses, Moehlig<sup>14</sup> advises two injections of 1 cc. each, given at three-day intervals a few days before the next period is due. Where irregularity of the rhythm is present, the first injection of pitressin tannate is given on the twentieth day after the beginning of the last flow.

In six cases of functional uterine bleeding, one or two injections of 1 cc. of pitressin tannate in oil controlled the bleeding.

No untoward results other than a mild headache have been observed. In patients with hypertension, nephritis, and cardiovascular disease, good judgment should be used, since it is quite possible

smaller doses than 1 cc. will prove effective. The hemostatic effect of pitressin tannate in cases of menorrhagia and metrorrhagia is explained on the findings of Greenblat, who concludes that excessive uterine bleeding will occur if the proximal (myometrial) portion of the spiral arterioles fails to constrict or be constricted following the initial extravasation of blood distally.

This report on the use of pitressin tannate in oil in excessive vaginal bleeding is an informal one.

**Menstrual Disturbances in Adolescent Girls** — Menstrual disturbances in adolescence consist of two varieties, those of rhythm and those of amount and duration of bleeding. Disturbances of menstrual rhythm are temporary states, since ultimately maturity of ovarian function establishes normal rhythm.

The author<sup>15</sup> approached the therapeutic problem of menometrorrhagia by a study of the vaginal smears in order to determine whether the bleeding occurred from an atrophic or from a hyperplastic endometrium. By this approach it was hoped to determine whether estrogens or progesterone was indicated. Both substances had been reported as effective therapy in menometrorrhagia. The estrogens would be indicated if the bleeding were occurring from an atrophic endometrium and progesterone if bleeding were occurring from a hyperplastic endometrium. The vaginal smear which indicates the presence of a hyperplastic endometrium is designated as Type IV (plaques of cornified epithelial cells) and the vaginal smear indicating an atrophic endometrium is the Type VIII (basal epithelial cells which are small and round with large vesicular polychromatic nuclei).

In cases where a Type IV smear was obtained, **progesterone** was used to convert the hyperplastic endometrium to the

secretory type and thus stop the bleeding. The administration of progesterone, it must be remembered, when interrupted is followed by a normal menstrual bleeding; therefore, the progesterone withdrawal bleeding should not be mistaken for a recurrence of metrorrhagia.

The case of a 14-year-old girl is presented to illustrate the therapeutic effects of progesterone on profuse bleeding of two weeks' duration. The vaginal smear was Type IV. Ten milligrams of oral progesterone was given daily for 14 days. The bleeding subsided, but did not stop. When therapy was interrupted the bleeding again became extremely profuse. The vaginal smear was nearly normal but the flow continued and a week later was again Type IV. Progesterone, 10 mg. daily, was injected on five consecutive days and on the fifth day the bleeding ceased. Two days later the bleeding recurred, diminished gradually, and ceased five days later. Nine normal periods, at four- to five-week intervals, have occurred since progesterone therapy was discontinued.

This therapeutic management was utilized in three more cases of menometrorrhagia. In one case a second series of progesterone injections were required to be administered at the subsequent period.

The author does not claim that progesterone will effect a cure; it is a therapy to tide the patient over a period until the patient's ovaries produce adequate quantities of progesterone.

The application of estrogenic therapy in persistent vaginal bleeding is illustrated in the case of a 15-year-old girl with a history of recurring bleeding and spotting for the past seven months. The vaginal smear was of Type III. She was given 0.1 mg. of **stilbestrol** orally each day. In three weeks the bleeding ceased and the stilbestrol was continued six weeks longer. The dosage was grad-



ually reduced until 0.1 mg. was given every third day. During the period of stilbestrol therapy the menses were normal. The normal rhythm was maintained for six months.

Two more cases of menometrorrhagia were similarly treated with stilbestrol preparations.

**Discussion**—While, in general, control of menometrorrhagia, regardless of its etiology, is possible by surgery or by giving large doses of male hormone, these types of therapy are undesirable. The problem was therefore investigated from the point of view of possible treatment with one or another of the female sex hormones. This proved possible, since the vaginal smear permitted determination of the cause of the bleeding. The smears obtained, respectively, from cases of hyperestrinism and hypoestrinism are so characteristic as to leave no doubt concerning the diagnosis.

This bleeding, in contradistinction to the bleeding for which the therapy is given, is self-limited and resembles that of a normal menstrual period. The use of progesterone should not be discarded simply because bleeding recurs upon withdrawal; such bleeding is expected.

The treatment may be continued until such time as the patient's own ovaries mature sufficiently to prevent the recurrence of menometrorrhagia.

**Summary**—Seven patients, aged 11 to 15 years, presenting the complaint of severe and/or prolonged menstrual bleeding, were studied by the vaginal smear technic. On the basis of the cell types in the smears, it was possible to separate the cases into two groups: The one to be treated with estrogen, the other with progesterone.

The bleeding in all patients was successfully controlled by the appropriate therapy.

## THE ENDOCRINES IN THE MALE

### Management of Male Pubescence

Schonfeld<sup>16</sup> states that the period of pubescence and adolescence in a boy is frequently associated with physical and psychological problems. The management of these problems requires an understanding of the mechanism of pubescence, if one deigns to classify normal from abnormal variations in order to institute proper management of the period of pubescence.

Normal development includes a prolonged period of latency in genital growth during which testicular growth does not progress because the hypophyseal gonadotropic hormones are only being produced in subthreshold amounts. This is designated as the period of prepubescence and terminates at the second decade when there occurs an increase in the output of the hypophyseal gonadotropic hormones, resulting in active stimulation and growth of the testes and increased androgenic production occurs as the consequence of increased activity of interstitial cells of the testes. The combined influence of the androgen and other factors of maturation stimulates the rapid growth and development of the penis, prostate, seminal vesicles, larynx, hair follicles, and epiphyses. The period of rapid growth is called pubescence. The period of pubescence terminates at puberty which Schonfeld defines as the period when the testes have matured adequately to produce spermatozoa.

In order to determine the normal range of variation accompanying the complexity of the process of growth and maturation in normal boys Schonfeld correlated the measurement of the penis and testes with the degree of maturation of the secondary sex characteristics in about 1500 males selected at random.



A chart illustrating the phases of individual development designates age five years as the start of the prepubescence period for all cases and it terminates at ages 11 years in the ninth decile group, at age 12½ years in the median group, and at age 15½ years in the first decile group. Puberty (fertility) occurs in the above respective groups at the following ages: Age 15½ years, age 16½ years, and age 17½ years. Postpubescence or adolescence, if defined as the period from puberty to full maturity, is reached approximately at age 19½ years by all groups but occurs in the age order of their reaching puberty.

An analysis of developmental events was determined and the above six stages of development and maturation were devised from the first stage including all prepubescent cases to the sixth stage which included only adolescent and physically matured individuals. The second stage contains all cases showing active growth of the penis and testes but no pubic hair, and the third, fourth, and fifth stages were primarily classified in accordance with the three stages of pubic hair growth (Crampton) and supplemented by the range of size of the penis and testes, and the state of development of the secondary sex characteristics. On the basis of this classification a decided variation in the normal physiological development for the various ages is determined. This analysis of normal puberal evolutions depicts that pubescence (stage 2) may normally begin at any age from 10 to 16 years, with isolated cases beginning later. Therefore, determination of the median or average age of onset of puberty is of no direct significance insofar as establishing the individual need of endocrine therapy for a hypogenital state, determined on the basis of the age of the average onset of puberty.

The author states the cognizance of these variations of normal is one of the most important factors in the management of the male pubescent. Realization of these factors excludes this group of prepubescents who are commonly classified as endocrine problems on the basis of the size of the genitalia, obesity, or growth.

In many obese cases, genital growth is at a normal age level but many cases are considered endocrine cases because the normal extent of penile growth is in part hidden from view by the fat accumulation about the pubic area. Elevation of the fat from the penile area exposes its actual normal size. Such obesity or pseudoFröhlich cases are metabolic problems which can be corrected by dietary restriction and suitable habits of activity and interest.

Apparently, Schonfeld does not consider *thyroid* therapy "to just below the toxic level of the individual" as endocrine therapy because he advocates this in conjunction with a *high protein diet*, *reduction of salts, fluids* to a minimum and *amphetamine sulfate* in 5 to 10 mg. doses, morning and afternoon to dull unsatiable appetites in the prepuberal obesity or pseudoFröhlich syndrome.

Schonfeld presents what he terms the rational approach to the treatment of the problems associated with pubescence based on controlled experience in a series of more than 750 cases in the endocrine clinics of Columbia-Presbyterian Medical Center and Morrisania City Hospital. He states there is no known endocrine product capable of initiating spermatogenesis.

Two main groups of endocrine substances were used for the male: The gonad stimulating (gonadotropic substances) and gonad substituting (androgenic substances). The gonadotropic substances included the anterior pitui-

tary gonadotropins, the chorionic gonadotropins of pregnant mare's serum, and human pregnancy urine. The androgen used was *testosterone propionate* and *methyl testosterone*. The physiological action of both of these types of hormones is the induction of pubescence; the chorionic gonadotropins stimulate the interstitial cells to produce androgens, while the androgens are substitutive agents.

In the prepubescent period, one is concerned with the ability of the testes to respond to future stimulation and the probability of the anterior hypophysis to initiate stimulation in due time. The actual size of the genitalia is of physiologic significance only after pubescence. Schonfeld uses what he terms indirect methods to evaluate the prognosis of future sexual development, since hormone assays have been found to be of no aid in the prepubescence. He maintains testing the responsiveness of the testes to large doses of chorionic gonadotropins (human pregnancy urine) would help evaluate both gonadal and hypophysial factors in pubescence. This response is expressed as an increase in circulating androgens and is clinically manifested by congestion and enlargement of the penis and subsequently the prostate. He states this response has often been misinterpreted in the literature as a therapeutic achievement.

The therapeutic test with chorionic gonadotropins is instituted as follows—500 to 750 international units three times each week for two or three weeks. This total dosage of potent chorionic gonadotropic fraction of human pregnancy urine is adequate to stimulate the testes but if no response is observed at the end of three weeks then 1500 international units are given three to five times each week for two or three weeks. He believes evidence of a positive response warrants

the assertion that the boy has at least one normal testis and probably adequate anterior hypophysial function so that he will have spontaneous pubescence if there is no abnormal change in his status.

In primary eunuchoidism, which the author defines as a condition occurring in children because of complete aplasia of the testes so that pubescence never develops spontaneously, he advocates the administration of 10 mg. of testosterone propionate by intramuscular injection three times each week or 30 mg. of methyl testosterone daily by mouth or a 150 mg. subcutaneous implant of testosterone. When testosterone propionate injections are used it should be increased as indicated to 25 mg. three times a week to induce pubescence. When full development for the individual age has been reached a maintenance dosage might be established and continued for life.

In secondary eunuchoidism, a state resulting from intrasellar or extrasellar pathology, the etiological factor should be determined when possible and controlled by surgery or x-ray therapy. If these measures fail and pubescence does not appear or if the etiological process cannot be eliminated, then only should androgens be used to induce pubescence.

The author's use of the term eunuchoidism as synonymous with hypogonadism is an unfortunate selection particularly when he speaks of eunuchoidal hypophysial dwarfism. In a footnote he states that eunuchoidism implies the inability of the individual to develop pubescence spontaneously rather than referring to the size and function of the genitalia.

Schonfeld determines this probability of reactivity of the testes to stimulation on the basis of the negative effect of large doses of chorionic gonadotropins administered as described. He has not found any active growth preparation:

therefore, he administers to these so-called cases of eunuchoidism, hypophysial dwarfism, a series of large doses of chorionic gonadotropins. If this therapy is not successful the treatment is directed toward the induction of pubescence with androgens. Androgen therapy in such cases is usually associated with a spurt of growth. In isolated cases of prepubescent boys ranging in age from 12 to 18 years large doses of androgen over a period of four to eight weeks were administered to induce pubescence and in such cases a spurt of growth has been observed. Treatment is stopped for three to six months to allow regression of the genital response and then a second or third series of treatment is given in hopes of stimulating growth spurts. This therapy for growth stimulation is considered experimental and not generally advised because of the liability of producing precocious puberty, premature closure of the epiphyses, and cessation of growth.

Gynecomastia is frequently a problem in the pubescent and every form of therapy has proven ineffective. Plastic surgery is advocated for gynecomastia except in eunuchoid cases where the gynecomastia is in a mild stage of development and in such cases androgen therapy had been helpful.

In the management of the psychogenic problems the administration of the chorionic gonadotropins or the androgens should not be maintained to the point that genital development advances above the normal limit or evoke uncontrollable emotional problems. When anxiety exists because of the underdeveloped genital state the rapid induction of pubescence by androgen therapy inflates the boy's ego.

The author concludes "chorionic gonadotropins and androgens are potent drugs capable of modifying both physical and emotional development of the male

pubescent. The judicious use of the substances requires an understanding of the physiological mechanisms of pubescence and the action of the various substances."

A great deal of therapeutic confusion has been created in the literature by the failure to appreciate the range of normal variations of genital size, age of onset of pubescence, and the characteristics of growth of the various types of body configuration (somatotypes). Many of these normal boys have been subjected to prolonged endocrine therapy with induction of pubescence, and their normal development is fallaciously attributed to endocrine therapy.

Obesity and growth should be considered without correlation with genital development and pubescence.

The management of the pubescent period is a most worthy and timely subject; it is a particularly important one now that active endocrine preparations for treatment of male hypogonadism are available.

*Comment* — Schonfeld<sup>16</sup> stresses the fact that one must have a knowledge of the variables of the normal pubescent period which normally may occur from 10 to 16 years in order to determine which cases should receive the benefit of endocrine therapy. While Schonfeld has laid down excellent guiding principles indicating the need of endocrine therapy in the treatment of delayed gonadal development in the pubescent period, he appears not to have adhered to the sound principles he advocates.

He states in discussing the prepuberal obesity or pseudoFröhlich syndrome that treatment limits itself to a slimming régime and the formation of new habits, activity, and interests. In his weight reduction program for the above condition, however, he states "thyroid must be given in the highest dose tolerated, which is just below the toxic level for the in-

dividual." The use of thyroid is advocated on its ability to increase basal metabolism, but this advice disregards the general physiological action of thyroid on calcium metabolism, its advancement of osseous growth to abnormal levels in the prepubescent period, as well as the fact the administration of thyroid to a point below toxicity releases from activity the normal physiological demands of the body on its own thyroid and the gland will go into functional atrophy. These are but a few of the harmful effects of administering thyroid extract to cases in whom *no deficiency of the thyroid activity exists*.

Subsequently, we are told about testing the male gonads of young boys, by the frequent administration of chorionic gonadotropins in large dosage, for their ability to respond subsequently to the activity of the anterior hypophysial gonadotropins when they are normally produced in the quantities which are then sufficient to advance the size and physiological activity of the testes. A positive test response from the administration of chorionic gonadotropin is clinically manifested by congestion and enlargement of the penis and subsequently the prostate, and on the basis of animal experiment an increase in circulating androgens occurs. This response of the underdeveloped testes we are advised has often been misinterpreted as therapeutic achievement; however, he defines it as a prognosticating therapeutic test and as a measure for differential diagnosis in bilateral cryptorchidism or delayed puberty from eunuchoidism. Unfortunately, Schonfeld uses the term eunuchoidism in an uncommon manner, namely, as a substitute for hypogonadism to imply the inability of the individual to develop pubescence spontaneously rather than referring to the size and function of the genitalia and the usually accepted clinical

picture of eunuchoidism. Thus, the usage of the terms primary and secondary eunuchoidism in children and eunuchoidal hypophysial dwarfism in children are not the accepted terms in common medical parlance of identifying the above clinical syndromes.

With these exceptions regarding his therapeutic conceptions of the problems this article is the first to attempt a rationalization of one of the most disputed fields of endocrine diagnosis and endocrines. Under such circumstances the opinions voiced concerning his presentation here should reflect only a minimum amount of detraction from the value of the paper and only be a supplemental effort to aid, as Schonfeld has admirably attempted, to clarify and rationalize a vexing problem.

**Functional Prepuberal Castration in Males**—Two new clinical syndromes have recently been delineated from the large and heterogeneous groups of adults with retardation or absence of sexual development. In the first group there is an associated short stature, retarded sexual development, and high urinary gonadotropin titers in women, and in the second group there is seminiferous tubular failure, gynecomastia, and high urinary gonadotropins in men. Heller, Nelson, and Roth<sup>17</sup> propose to add a third group which has many features with the syndrome (Group 1) described by Kenyon, but occurs in males.

The syndrome, in the opinion of the authors, may be regarded as a functional prepuberal castration. The characteristic features of the new syndrome as observed in the six cases were: (a) Presence of wolffian duct structures in the scrotum, but absence of functional testes; (b) infantilism: high-pitched voice; sparse pubic hair; absence of body, extremity, and facial hair; infantile penis and scrotum; presence of erections but

absence of ejaculations; small, underdeveloped prostate gland; (c) stature; the excessively tall eunuchoidal type of height was not observed; the stature tended to be normal or short; (d) eunuchoidal statural proportions were observed in four cases; (e) moderate delay in osseous development, delay in formation and closure of the epiphyses and small or rudimentary frontal sinuses; (f) gynecomastia was observed clinically in three cases and breast biopsies in all six cases revealed histological evidence of departures from normal male breast; (g) high urinary titers of gonadotropic hormone with values comparable to that of the surgical castrate; (h) low normal or subnormal excretion of 17 ketosteroids and estrogens. The syndrome showed a negative response to the *chorionic gonadotropins* but a positive response to *testosterone propionate*.

All the patients were in a good state of health and the age range was from 19 to 57 years. The routine laboratory studies showed no essential departure from the normal. The tabulated clinical features show that three of the six cases were obese, 160, 190, and 220 pounds, and two cases were underweight. The maximal length of the penis was 1.5 inches and gross testes size observed in the two cases in which they were palpable was equal to a navy bean in one case and a pea in the other case. Microscopic study of these testes showed atrophic structures, essentially composed of collagenous fibers with scattered hyalinized areas in one case; the second case showed essentially the same picture with scattered patches of sclerotic seminiferous tubules, a number of which showed spermatogenesis, spermatocytes, and spermatids. Erections could be produced "at will" in all six cases.

The gynecomastia, duration 8 to 20 years, observed in three cases was con-

sidered to be true gynecomastia on the basis of the histological studies of the breast biopsies. However, the number and size of the ducts were only slightly increased over the normal; the presence of bud and alveoli was regarded as the significant and determining diagnostic factor. These findings are a departure from the normal breast but are consistent with the histological findings in the breasts of some senile males.

**Therapeutic Results** — The general plan of therapy was the administration of 25 mg. of testosterone propionate five times weekly for three to four months. A summary of the general order of response of the patients to the testosterone therapy was: Increased number of erections within the first week of therapy; ejaculation (aspermatic) usually occurs by the third week; the voice changes in from two to four weeks. The genitalia begin to increase in size by the tenth day and continue to increase in size for many months. The wolffian duct structures, when present in the scrotum, increase in size and often simulate small testes. The prostate gland increased to nearly normal size in three months. The obese patients tend to lose weight and the thin ones to gain weight. Hair growth, except facial, is increased, being first observed in two to four weeks in the pubic region and last observed in three to four months at the umbilical-pubic line. The antisocial attitude of these patients changes to the gregarious. The authors believe continuous therapy is not required; rest periods of from two to four months are advised. The general therapeutic plan suggested is alternating three-month periods of hormonal administration and rest.

Assay studies conducted during the periods of testosterone therapy revealed a definite and fairly rapid fall in the secretion of gonadotropins; however, the

individual responses showed some variation. In three cases the urinary gonadotropins remained higher than normal.

Excretion of 17 keto-steroids was not altered significantly by the administration of testosterone propionate; however, the excretion of estrogen, which was lower than normal prior to testosterone therapy, rose to approximately normal levels during treatment with androgens. The authors believe this rise in estrogens may represent metabolites of the administered androgen.

This new syndrome may arise from a variety of causes. The authors believe their cases present at least three different etiological factors; two cases are considered to be examples of atrophy of the testes due to a sclerosing process; one case—postoperative atrophy of the testes charged to surgical interference to the blood supply during operation for bilateral cryptorchidism at age five years when a very small testis was found, and the other three cases the failure of union between the wolffian duct derivatives and the testis with only the former descending into the scrotum is regarded as the most plausible explanation of the failure of gonadal development to occur.

The variability of pubic and axillary hair growth in cases of eunuchoidism is related to the variance of 17 keto-steroids excretion observed in the various cases. The 17 keto-steroids are obviously not of gonadal origin and probably originate in the adrenal cortex.

The statural variation of the functional prepuberal castrate who is short or normal from the tall eunuchoid is explained on the basis that the former has no testicular androgens whereas the tall eunuchoid individual has a minimal or reduced amounts of testicular androgens, and this may be sufficient to cause bone growth without sexual maturation.

The breast changes observed in these cases are similar to those observed in patients with hyalinization of the seminiferous tubules (Group 3). In both instances the excretion of estrogens tends to be subnormal for the male. This reduces the factor that estrogenic hormone is responsible for the mammary changes. The factors postulated by Klinefelter, Rufenstein, and Albright as being responsible for the gynecomastia in their cases were: The normal seminiferous tubules elaborated estrogen and this prevents gonadal testosterone from stimulating mammary growth. Later they substituted "inhibin" for estrogen. When hyalinization of the seminiferous tubules occurred and estrogen is not produced the gonadal testosterone is uninhibited and mammary growth occurs. The authors state this explanation is inadequate for their cases with gynecomastia, since neither inhibin or testosterone could have been secreted by the gonads. This leaves only the possible mammogenic activity of the 17 keto-steroids to account for the mammary changes.

Testosterone therapy had no marked effect upon the size of the breast in their cases. In one treated case the histological study tends to indicate that testosterone propionate tends to discourage rather than stimulate mammary growth.

**Comment** This is a valuable contribution to clinical endocrinology. This opinion is based not upon the fact that a new hypogonadal-growth syndrome is presented but because the general hormonal studies treated and untreated in these cases clarify certain factors concerned in human growth and the occurrence of gynecomastia or breast hypertrophy in the male.

In this group of patients with presumptive evidence of absent or physiologically inactive testes the height of the patient was normal or short; however,



the proportionate measurements were of eunuchoidal character. The average eunuchoidal individual is taller than normal and may even be a giant. The disparity of height in the two types of eunuchoidism is attributed to the fact that the average tall eunuchoidal individual possesses some degree of gonadal development and accordingly is receiving small amounts of gonadal androgens. These gonadal androgens even though minimal and of a quantity insufficient to induce sexual maturation are, nevertheless, in their opinion, sufficient to contribute an effect on growth stimulation. This is an important point, since if it is true that small amounts of androgens can stimulate growth, the use of large or even moderate dosage of the testosterone preparations in the cases of retarded growth occurring during childhood and adolescence is contraindicated. This opinion is in accord with our personal experience, namely, that in cases of retarded growth associated with hypogonadism, it is best to administer testosterone preparations, *methyl testosterone* or *testosterone propionate*, at a dosage level which produces a very gradual stimulation of sexual development.

In regards to gynecomastia it cancels out proposed etiological factors; further illustrates the negative effect of testosterone therapy in gynecomastia and increases the necessity of evaluating and indicating the source of the 17 ketosteroids in the various endocrinous syndromes.

This new syndrome is of interest because of the consistent finding of wolffian duct derivatives in the scrotum and the absence of testicular tissue or presence of atrophic testicular tissue. The stimulating response of the testosterone propionate on the wolffian duct tissue and the accompanying increase in size of the scrotal contents is a warning against

attributing the growth of the wolffian duct tissue as an increase in size of testes when testosterone is administered. The therapeutic studies conducted in the cases again illustrate that the chorionic gonadotropins are ineffective agents for stimulating hypoplastic human gonads.

**Testosterone Therapy of Male Eunuchoids**—Lisser and Curtis<sup>18</sup> present evidence of the effectiveness of the sublingual method of administration of *methyl testosterone*. The form of sublingual therapy used was a compressed tablet containing 5 mg. of methyl testosterone. The tablet was placed under the tongue and kept there until dissolved. From 15 to 30 minutes is required for the highly compressed tablet to dissolve and during this period the patient was instructed not to swallow or expectorate. An alternate method is to place the tablet between the second molar and the cheek.

Twelve patients were treated with lingual methyl testosterone therapy. Six of the patients had been treated with testosterone, administered parenterally or by implantation, by tablets perorally or by solution sublingually for a sufficiently long period of time to permit critical comparative appraisal of the effectiveness of the various forms of therapy.

CASE 1: Age 24 years, presented the characteristic picture of preadolescent eunuchoidism. He had received implants of testosterone, doses 143 to 800 mg., between April, 1940, and May, 1941. Between May, 1941, and April, 1942, he had been administered either methyl testosterone (perorally), testosterone propionate (hypodermatically), or free testosterone dissolved in propylene glycol, sublingually administered in 5-mg. doses. On the latter therapy, administered for the last 11 months, he had lost ground somewhat in the subjective sphere of therapeutic relief, although there had been no regression in the size of the external genitalia.

The administration of 20 mg. of methyl testosterone were required to maintain this patient in a satisfactory subjective and objective status. The administration of 10 or 15 mg. daily was



found to be inadequate therapy. In this patient the effect from 20 mg. of methyl testosterone linguinally administered was considered to be equal to 30 mg. of methyl testosterone administered perorally.

The penis developed considerably during the 10-month period that linguet therapy was administered.

**CASE 2:** A typical eunuchoid, age 24, required 30 mg. daily, perorally, of methyl testosterone to maintain the subjective and objective improvement produced by 3500 mg. of testosterone propionate which had been administered parenterally during a period of 16 months, and five implants of testosterone, dosage 101 to 164 mg. per implant, during the following year.

For a period of 11 months, to April, 1942, 15 mg. of free testosterone, dissolved in propylene glycol and administered sublingually, was found to be as effective as the 30 mg. of methyl testosterone administered perorally.

In April, 1942, he was administered 15 mg. of methyl testosterone as linguets. In September, 1942, the dosage was reduced to 10 mg. daily, and this dosage was found adequate to insure satisfactory intercourse once a week. The size of the genitalia remained the same. The period of observation for the linguet therapy was six months.

In one case of preadolescent eunuchoidism, age 31, and another, age 24, who had received essentially the same therapeutic management as the two former cases it was found that eventually the dosage of linguet therapy could be reduced to 5 mg. daily. The periods of observation for the linguet therapy were six and seven months.

**CASE 5:** Age 29.5 years. Had infantile genitalia and essentially lacked secondary sex characteristics. He had received no other testosterone therapy other than testosterone compounds dissolved in propylene glycol and administered sublingually in 12.5 mg. daily dosage. The subjective and objective improvement obtained with this form of therapy in 12.5-mg. doses during a period of 10 months was stated to be equivalent to that produced by 50 mg. of perorally administered methyl testosterone.

For a period of 10 months this patient received linguet therapy, at first 10 mg. and subsequently 5 mg. The authors state that in this typical 30-year-old eunuchoid, one 5-mg. linguet of tes-

tosterone per day maintained a satisfactory status, both subjectively and objectively.

Excellent results from the linguet therapy were obtained in a 19 $\frac{1}{2}$ -year-old male with bilateral cryptorchidism and lack of secondary sex characteristics. He was administered 15 mg. daily of linguet methyl testosterone and in a period of 3.5 months he gained 25.5 pounds, and the penis developed from 4.5 cm. long by 6.5 cm. in circumference to 9 cm. long by 10 cm. in circumference. Erections occurred two or three times daily and he felt much stronger and energetic. The testes could not be felt. A marked general improvement in his appearance also occurred.

Linguet therapy was administered to a 73-year-old male who promptly developed symptoms of the male climacteric after bilateral orchidectomy performed following injury to his testes.

**Discussion** The purpose of this investigation was to determine whether highly compressed tablets of methyl testosterone, designed for slow sublingual absorption, would: (a) Maintain the improvement previously produced and maintained in cases of severe eunuchoidism by administration of testosterone propionate intramuscularly, by implantation of methyl testosterone pellets subcutaneously, by administration of methyl testosterone tablets perorally, and/or by the sublingual absorption of testosterone dissolved in propylene glycol; (b) initiate an improved sexual status subjectively and objectively in hypogonad individuals who had not previously received any form of testosterone therapy; (c) reveal the advantages or disadvantages, economically and otherwise, of the use of linguets as compared to parenteral, implantation, peroral, or the absorption sublingually of a testosterone solution.

The effectiveness of methyl testosterone linguets as a maintenance régime

was tested in seven patients, all of whom had been typical examples of severe pre-adolescent eunuchoidism and who had been exceedingly immature at the ages of 24, 24, 31, 24, 29.5, 21, and 35 years, respectively. At the time methyl testosterone therapy in the form of linguets was initiated they had been vastly improved by other forms of testosterone therapy. They had reached the ages of 26, 29, 35, 26, 30, 26, and 36 years, respectively.

**Summary**—Twelve males, whose ages ranged from 19 to 73 years, were victims of severe hypogonadism. Nine of these 12 patients had never matured; one had matured partially; one suffered from testicular deficiency secondary to acromegaly; one had been castrated at 72 years of age. Some of these patients had been treated previously by other modes of testosterone therapy. All were well maintained on much smaller amounts of testosterone compounds when methyl testosterone was administered in the form of 5 mg. linguets designed for sublingual absorption. In 6 of the 12 patients, one 5 mg. linguet daily sufficed for maintenance, a remarkably small dose. Only 15 mg. daily of methyl testosterone in linguets produced striking genital improvement in a 19-year-old lad suffering from severe eunuchoidism and who had never had any other form of testosterone therapy. He gained 25.5 pounds in 3.5 months.

Methyl testosterone linguets in the form of 5 mg. hard compressed tablets for sublingual absorption is to date by far the most economical mode of administering androgens to hypogonad males.

**Therapy of Seminal Inadequacy**—This report<sup>19</sup> concerns 21 patients with seminal inadequacy whose pretreatment, treatment, and post-treatment seminal levels are judged to have been established accurately and whose trials of therapy

are regarded as having been well controlled. When hypometabolism was present thyroid therapy was administered, and hygienic and dietetic deficiencies were corrected.

The therapeutic schedules employed included: *Pituitary, chorionic, and equine gonadotropins* singly; *combined therapy with pituitary and chorionic gonadotropins*, and *combined therapy with equine gonadotropin and testosterone propionate*. The usual schedule embraced daily intramuscular injections for six weeks with a rest period of corresponding duration before additional treatment was given. The majority of patients received more than one type of gonadotropin and more than one series of treatments.

The periods of observation of the patients varied from 3 months to 5½ years.

The ages of the patients ranged from 27 to 43 years. None of them exhibited signs of pituitary or androgenic deficiency. They were classified into three groups on the basis of physical findings: *Group I*, those with normal urologic findings except for seminal inadequacy (cases 1 to 12); *Group II*, those with apparent partial atrophy of one or both testes but with no evidence of androgenic deficits (cases 13 to 16); *Group III*, those with chronic epididymitis and chronic prostatitis (cases 17 to 21).

Despite reports by other workers of apparent improvements in seminal values incidental to therapy with various gonadotropins, the authors' data provides no evidence that significant enhancements of seminal function were associated with the treatment schedules employed. They employed chorionic and equine gonadotropins in doses which were as large as, or larger than, those commonly used and which should have been adequate as judged by their ability

to evoke specific ovarian responses in the female. The doses of pituitary gonadotropin were admittedly inadequate, due to the low potency of available preparations. Responses to therapy were sampled by seminal studies during the last week of treatment and after six weeks of rest from treatment.

The employment of the total number of motile spermatozoa in an ejaculate as a criterion for evaluating therapy appears justified and practical.

Of the five patients whose seminal values improved during therapy, three had received pituitary gonadotropin and two equine gonadotropin.

Analysis of data failed to demonstrate that gonadotropic therapy improves any particular factor studied in the seminal examination, either volume, number of spermatozoa, morphology, or immediate motility. Furthermore, there was observed to be no correlation between the degree of seminal impairment and the effectiveness of therapy.

**Summary**—Twenty-one male members of childless couples with seminal inadequacy, whose ages (when first seen) ranged from 27 to 43 years and the duration of whose sterile matings ranged from 2 to 15 years, were investigated and treated with various gonadotropins.

Twelve patients presented no signs of andrologic disease; four had partial atrophy of one or both testes; five gave evidence of chronic epididymitis and/or prostatitis. None presented symptoms or signs of pituitary disease or androgenic deficiency.

The following therapeutic schedules were employed (average series comprised six weeks of daily injections): Chorionic gonadotropin, 16 series, average dosage for series 12,600 I.U.; pituitary gonadotropin, 11 series, average dosage for series 10,800 R.U.; equine gonadotropin, 8 series, average dosage

for series 9700 I.U., and in addition six combined series of pituitary and chorionic gonadotropin and five combined series of equine gonadotropin and testosterone propionate.

Analysis of treatment data which took into account spontaneous fluctuations of values of various seminal factors failed to establish any significant enhancement of seminal values relatable to therapy, despite the fact that the wives of four patients became pregnant.

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## THE MALE CLIMACTERIC

The male pituitary gonad cycle is influenced by castration, hypofunction, or afunction. These states deprive the system of the normal amount of sex hormones and are liable to be followed by the various endocrine and autonomic system imbalance which produces the subjective and objective symptoms of the male climacteric. These symptoms vary from mild to extreme; in the latter state the patient may become psychotic (involuntal melancholia).

**Symptoms** The climacteric syndrome is a functional state. The type of symptoms of the climacteric are the same for the female and the male, and may be classified as: (1) Nervous; (2) circulatory, and (3) general.

The nervous symptoms are: Nervousness, feeling of tension and inward tremulousness; fatigue or excitement accentuate it and then a tremor may be noticeable. Irritability is present and they are easily excited to anger by word or deed. They are hard to get along with.

Excitability is a nervous state; the ordinary stimuli produce an exaggerated psychic response. The patient sleeps poorly and restlessness during the night is common. The interrupted or brief periods of night rest leave them exhausted during the day and day rest is required.

Formication, itching, prickling, tingling, numbness are complained of, especially of the extremities.

Headaches, dull to severe in type, may occur irregularly or be continuous. The temporal, frontal, vertical, or occipital region and particularly the vertex and occipitocervical regions are the usual sites for headache of the hypogonadal patient. The occipitocervical headache may radiate down the neck and last from hours to days. The mind is hazy or fogged.

Memory and ability for concentration are decreased. Depression or mild melancholia may occur and the patients lose interest in work, home, and in social life. Emotional outbursts and crying may occur, self-confidence is lost, and then a sense of futility occurs. The circulatory symptoms are hot flushes, redness of face, neck, and chest, and frequently a smothering sensation is complained of. Chilliness may be a complaint and they may be awakened from their sleep by tachycardia and palpitation. Hypertension and cardiovascular disease if present is aggravated. Vertigo, tinnitus, and scotomata may be present.

General symptoms consist of lassitude, fatigability and lack of endurance. Potency and libido vary, the latter because it is under the influence of mental reaction and may be present in the absence of potency.

Distention and eructation may occur after meals and constipation is frequently complained of. The nervousness adds to and aggravates the gastrointestinal symptoms.

The symptoms of the climacteric occur not only at the normal period but they may also occur when there is a marked decrease in the amount of androgenic hormone present during the period of active sexual life.

Thirty-seven patients, two eunuchoids with cryptorchid testes, three hypogonads, two cases of atrophy of the testes (surgical one, x-ray one), and 27 climacterics (three involutional psychosis) were studied. The average age when medical attention was first sought was 53 years and the ages varied from 41 to 64 years. Obesity was not frequently observed. The average pulse was 68 per minute. The average blood pressure was 130/86 mm. of Hg. The highest systolic pressure was 190 and the lowest diastolic pressure was 70. The B.M.R. was minus 16.6 per cent in 26 patients. Potency was decreased in 94.9 per cent and libido was absent in 46.9 per cent of the patients.

**Therapy** — Twenty-six patients received intramuscular injections of 10 mg. or 25 mg. dosages of *testosterone propionate* every other day. Twenty-four of the 26 patients were available for complete report and all were benefited by relief of symptoms and a sense of well being.

**Discussion and Conclusions** — The paper<sup>20</sup> represented a study of 37 male patients, each of whom had one of the types of testicular hypofunction or afunction which can be, or is, the etiological factor in initiating the hypogonadal or climacteric syndrome described above. Except for disturbances of menstrual function in the female, this syndrome is the same in both sexes, and varies in each individual of either group, according to the constitutional, functional, and mental make-up.

To make the syndrome more easily interpretable in these patients, an attempt was made to describe each symptom, as it was complained of to the author by a great many patients of both sexes.

Testosterone propionate is effective in relieving these symptoms in the male,

just as estrogens are in relieving the similar syndrome in the female.

Occasionally a patient is found, who, when relieved of his symptoms, is disappointed because potency has not been restored to his own satisfaction. It might be well to add a word of caution on this point. It is questionable whether androgens should be administered to promote potency; at least, the return of potency should not be promised to the patient, and he should be advised that decrease of potency is a normal consequence of age and that the chief objective of treatment is relief of the symptoms.

**Angina-Like Pain** — McGavack<sup>21</sup> states that until further hormonal studies are available which establish definite relative values for gonadotropins, estrogens, and androgens during the climacterium, the subjective complaints of the patient will be of paramount importance during therapy.

In addition to the generally recognized group of symptoms of the male climacteric the author adds the cardiac syndrome, already well recognized in the female.

The clinical features by which we may recognize the cardiac syndrome in the male climacterium appear to be:

1. Dull, constant oppression over and to the left of the sternum.
2. A sense of uneasiness and insecurity throughout the chest.
3. Attacks of anginalike pain, not necessarily related to effort and not relieved by nitroglycerin.
4. Breathlessness totally unrelated to effort or to time of day or night.
5. Long, sighing respirations, explained by the patient as an effort to relieve the sense of uneasiness in the chest.
6. Paresthesias of various parts of the body, varying from a feeling of numbness to sharp, lightninglike pain, and distinguished from other types of pain by the fleeting nature and tendency to migrate rapidly from one part of the body to another.

7. Palpitation or sense of palpitation without any change whatsoever in the heart rate.

8. A depression of the S-T segment in all three limb leads of the electrocardiographic tracing.

9. Associated symptoms suggesting the climacterium, such as general mental and physical weakness, easy tiring; myalgic and arthralgic pains; digestive disturbances without evidence of disease in the gastrointestinal tract; mild urinary symptoms, including loss of force of urinary stream, terminal dribbling, and vague lower abdominal distress.

10. Prompt relief of all symptoms, usually within 24 to 48 hours, following the parenteral administration of a testosterone preparation.

The subcutaneous injection of 25 mg. of *testosterone propionate* produced complete relief of the cardiac neurosis symptoms within 24 hours. If other climacteric symptoms were present such as weakness, listlessness, pain, diminished libido, and shortness of breath, not related to exercise or time of day, the injections were repeated every two or three days. When testosterone therapy caused disappearance of all the symptoms, *implantation* therapy was substituted in cases where continuous *hypodermic testosterone therapy* was indicated and *oral testosterone therapy* would be inadequate as a substitute for injection therapy.

The relief of symptoms obtained in 8 cases by the administration of testosterone when other measures failed, in the opinion of the author, seems to leave little room for doubt as to the origin of the symptoms. On the basis of the history and the physical findings alone, organic disease cannot be eliminated as a diagnostic possibility in these and similar cases. Therapeutic tests with nitroglycerin and testosterone will be helpful in distinguishing one from the other. Testosterone therapy may activate libido to an undesirable level and become a factor in producing a serious complication. Impotence was not a feature in five

cases, and was of slight degree in one of the three others.

In applying testosterone therapy to the specific type of cardiac complaint which it is capable of relieving, it would seem to be of more than academic interest to make the distinction between the cardiac neurosis of the climacterium and an organic lesion.

The mode of action of gonadal hormones upon the heart and circulation is not entirely clear. Estrogens and testosterone are vasodilating agents under certain conditions, and testosterone is a vasoconstricting agent in other circumstances. The phasic action of testosterone is of more than passing interest in this connection. "We have observed aggravation of precordial pain from larger doses too frequently administered. Moreover, while an effect in lowering blood pressure is commonly observed, in our experience previously normal values have been elevated to hypertensive levels by the too vigorous use of the drug."

The action of the vasodilator drugs can usually be detected in from several minutes to two to three hours; that of testosterone, in not less than several hours.

**Summary**—Severe angina-like pain was observed in eight patients who did not respond to treatment with vasodilator drugs and sedatives, but were promptly relieved by the administration of testosterone. When looked for, other evidence of changing testicular function was present, such as impotence, easy tiring, myalgic and arthralgic pains, vague digestive complaints, mild genitourinary symptoms, insomnia, and vasomotor disturbances. As a group, these patients represent a syndrome in which some cardiovascular disturbance, notably precordial pain, is the predominant expression of the male climacterium. Their failure to respond to the usual vasodilator drugs distinguishes them from other

forms of angina pectoris which may or may not be relieved by sex hormone therapy.

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## THE PITUITARY

**Treatment of Gigantism**—The ultimate height reached in gigantism may be influenced by many variables among which are: the height of the parents; nutrition and systemic diseases; the age of onset; the duration of the hyperpituitary state; the time of epiphyseal closure, and the hypersecretion or hyposecretion of the other pituitary hormones.

Normal or hypoplastic gonadal development may be present in giantism. Numerous complicating disorders of the endocrine or nonendocrinous origin may be present.

Gigantism is not only a medical problem but also an economic and social problem, therefore an attempt to retard or arrest growth should be undertaken.

The report<sup>22</sup> concerns a case of gigantism first examined at age 15 years and the clinical course observed for six years.

At age 15 years he gave a history of having grown six inches during the past six months. His height was 6 feet 6.25 inches. The genital development was markedly subnormal and secondary sex characteristics were absent.

The B.M.R. was —19 and —22 per cent and the blood cholesterol never exceeded 170 mg. per cent per 100 cc. of blood. The x-ray study showed an enlarged sella turcica and open epiphyses.

**Therapy** — Roentgen-ray therapy was administered intermittently for 5.5 years. During this period of time the sella turcica decreased from 23 by 19 mm. in 1936 to 19 by 13 mm. in 1942. Each x-ray treatment consisted of 300 r and during the 5.5 year period the patient grew nine inches. The patient showed a marked variation in height growth from time to time; thus the effect



of the roentgen ray therapy in retarding growth might be questioned.

At age 18 years, no progress in gonadal development having been observed, an attempt was made to stimulate gonadal development and development of the secondary sex characteristics by administration of 1500 R.U. of *chorionic gonadotropin* and 150 R.U. of *pituitary gonadotropic factor* daily for six days of the week. The total weekly dose of chorionic gonadotropin was 9000 R.U. and pituitary gonadotropic factor 900 R.U.

This therapy was maintained for 8½ weeks, but was given in a course of four treatments. The total dosage was 300,000 R.U. of chorionic gonadotropin and 30,000 of anterior pituitary gonadotropin factor.

Two months after beginning the first series of injections an increase in size of the penis and testes were observed and an occasional erection was noted. Pubic hair growth was long by the third course of treatment. At the end of one year after beginning the chorionic-anterior pituitary gonadotropin therapy there was definite regression in the size of the penis and testes and very little pubic hair remained. This regression had begun six months after beginning therapy.

*Testosterone implants* were started one month later and 150 mg. of testosterone were implanted subcutaneously every four months for five implants, except the third implant, which was 300 mg. of testosterone.

The total dosage of testosterone implanted subcutaneously during the 15-month period was 900 mg. and this produced a marked development of the penis and pubic hair.

Neither the gonadotropin therapy nor the testosterone therapy gave evidence of stimulating growth and the latter ex-

hibited a more positive effect on epiphyseal closure.

The x-ray therapies were succeeded by a definite state of lassitude which responded to 5 mg. of *benzedrine* twice a day. The patient always felt better after the effects of the x-ray treatment wore off.

In reviewing his experience with this case the author concluded that in future attempts to limit growth in such cases, he would give roentgen-ray therapy for a few months in the hope that genital development might take place, and if so, the roentgen-ray therapy would be maintained as long as such continued. If no such development resulted within three to six months, then surgical removal of the adenoma would be advised. If this procedure were not followed within a few months by genital development, testosterone therapy would be instituted at once. If surgery were refused, both roentgen-ray therapy and testosterone should be given. If when first seen, the patient's growth had reached a height which, with a few more inches of growth, would burden him with all of the difficulties which beset a real giant, surgical removal of the tumor would be justified as soon as possible.

**Conclusion**—A case of pituitary gigantism is presented. Stimulation of genital development occurred with combined pituitary gonadotropic and chorionic hormone injections; regression followed its discontinuance. Thereafter testosterone implantations produced genital development and epiphyseal closure, thus arresting longitudinal growth. Roentgen-ray therapy appeared to have been effective in retarding growth when it was first used. Early operation is urged on these cases if other measures fail to promise cessation of growth.

**Abscess Within the Sella Turcica Simulating Pituitary Tumor**—This



report, according to the authors,<sup>23</sup> is the first primary abscess in this location. There are reports of secondary abscesses within the sella turcica arising from primary abscess in other parts of the body.

The patient, a white female, age 34 years, complained of severe headache and vomiting. At age 18 years she developed headaches which were relieved by removal of a series of polyps obstructing the nasal passage. She was married at age 20 years and had a normal delivery at age 21 years. Menses were irregular for five months postpartum and thereafter ceased entirely. Also during the immediate postpartum period diabetes insipidus developed, which was relieved by *pituitrin* when employed. There was some amelioration of the severity but the condition essentially persisted.

At age 31 years she began to experience severe attacks of left-sided headache which extended from behind the left eye and over the head into the nuchal region, and which occurred daily in the afternoon. Blurring of vision without diplopia, and nausea and vomiting occurred during the height of the attack. Recently she had noticed that her left field of vision was limited and that auditory acuity in the right ear was diminished.

The patient's examinations revealed a female of normal habitus and normal distribution of hair. Blood pressure and pulse were normal. Cocainization of the nasal mucus failed to relieve the headache. Ophthalmic examination—fundus, normal; bitemporal hemianopsia, marked degree. Hemoglobin—12.5 Gm. per 10 cc. Erythrocytes 4,430,000; leukocytes 10,300. Basal metabolic rate minus 13. X-ray—sella enlarged with some erosion of the floor in the anterior portion. Diagnosis of "chiasmal lesion" was made by Love and operation to remove pressure

from the sella turcica and the optic chiasma was advised. *A right trans-frontal craniotomy*, using intratracheal ether, was performed, with the following findings: Abnormal mass situated anterior to the optic chiasma and between the optic nerves. After exploration of mass by needle and the presence of pus was determined, a cannula was inserted and 15 cc. of greenish yellow pus was evacuated (culture of pus subsequently reported sterile). Capsule of the abscess opened and *sulfanilamide* was placed within the abscess cavity and about the optic nerves and drainage established, followed by closure.

The postoperative period was rather uneventful except for a temperature, but the convalescence was complicated by a sudden attack of anesthesia and paralysis on the left side involving the face and extremities. The symptoms vanished spontaneously within a few days except for facial weakness. The foregoing episode was concluded to be the result of a vascular spasm involving the right side of the circle of Willis.

One year later the patient's eyes showed excellent improvement and the diabetes insipidus was well controlled by nasal insufflations of *pituitary powder*. Slight left facial weakness persisted. In two years her condition was excellent except for very slight left facial weakness.

In commenting on their case the authors state that with a history of disturbance in menstrual cycle (frequency excluded), or absence of menstruation and disturbance of water metabolism, or the presence of diabetes insipidus and a disturbance of vision exists, constitutes presumptive evidence that a pituitary tumor is present, or at least that a lesion situated above the optic chiasm is interfering with the function of the pituitary body and also with the visual pathways.

Supporting the diagnosis was the finding of erosion of the floor of the sella turcica and typical bitemporal hemianopsia. The unusual symptoms of pituitary tumor were headache and vomiting. In their opinion headache and vomiting accompany pituitary tumors only when the pituitary tumor is of sufficient size to make it project above the sella and encroach upon the third ventricle and thereby interfere with the circulation of the cerebrospinal fluid.

The use of sulfanilamide was deemed necessary because of the pus and it was packed into the sella turcica to control infection since infection could not be limited otherwise. This procedure, *i. e.*, the sulfanilamide crystals, was held to account for the complications (neurological) experienced during convalescence and this event would discourage them from using sulfanilamide in this manner again.

**Comment**—This patient apparently did not exhibit any signs of myxedema or severe hypothyroidism in spite of the pituitary abscess. Presumably there was a considerable amount of functioning anterior lobe remaining and it is probable since there was an associated diabetes insipidus the lesion was located in the posterior portion of the anterior lobe.

**The Pituitary Antidiuretic Hormone in Diabetes Insipidus**—The report<sup>24</sup> concerns the clinical course and therapeutic results obtained with the various posterior lobe preparations in diabetes insipidus. The cases reported had had diabetes insipidus for a period of years, and during their illness had used posterior pituitary extracts in various forms, orally administered posterior lobe dry extract, hypodermic administered pituitrin and pitressin, and intranasal application of powdered extract of posterior lobe and the liquid extract of pituitrin. Ultimately all patients were treated

with *pitressin tannate in oil* and this was found to give the most satisfactory results as well as causing the patient the least therapeutic inconvenience.

The antidiuretic hormone of the posterior lobe normally present in the circulation causes an excretion of about 1500 cc. of urine per day. When too much antidiuretic factor is administered, oliguria with water intoxication results. The oliguria is accompanied by rapid weight gain, headache, restlessness, vomiting, and convulsions.

The case of diabetes insipidus when restricted to a normal amount of fluid intake becomes dehydrated and the specific gravity of the blood increases. The patient then complains of headache, fatigue, muscular pain, hypothermia, rapid loss of weight, tachycardia, and finally collapse with psychic disturbances.

The posterior lobe hormone causes a rise in urinary chloride concentration, elevation of blood pressure, blanching of the skin, palpitation and headache, increased peristalsis, with bowel evacuation and uterine contractions. Urinary excretion is at first increased and later it is diminished. About 5 per cent of patients are refractory to posterior pituitary lobe. The following dosages were utilized in the various cases.

A single injection of 0.5 cc. of pitressin tannate in oil gave complete relief for 24 hours and partial improvement for 24 hours. An injection of 1 cc. gave complete relief for 48 hours and partial relief for 72 hours, while 2 cc. gave complete relief for 96 hours. When completely relieved from thirst the 24-hour urine was about 1500 cc. as compared with 7500 cc. without treatment.

**CASE 2:** Female, 7½ months pregnant; excreted up to 12,500 cc. of urine. One cc. of posterior pituitary solution was ineffective therapy, giving only partial relief and urination occurred every two hours at night. Daily injections of 1 cc. of pitressin tannate in oil gave

complete relief of symptoms with elimination of 2000 cc. of urine daily and nocturia disappeared. Extreme nervous stress would increase urinary output to 10,000 cc., although she had taken her daily injection of pitressin tannate.

CASE 3: A female, age 28, excreted 15,000 cc. to 20,000 cc. of urine in 24 hours and had nocturia eight times per night. She was four months pregnant and she had had diabetes insipidus for many years. Her sister (an identical twin), father, grandfather, and father's sister all had diabetes insipidus. Daily injections of five units of pitressin tannate in oil reduced the urinary output to 3000 cc. in 24 hours.

CASE 4: The twin sister of Case 3. Her diabetes insipidus was only 50 per cent as severe as her sister's and she refused therapy.

CASE 7: Female, age 47. The 24-hour urine was measured and pitressin tannate in oil was injected as recorded on the following dates: December 17, 1942, 4000 cc.; December 18, 3500 cc.; December 19, 6000 cc.; January 21, 1943, 0.5 cc., 2500 cc.; January 25, 1 cc., 750 cc.; January 26, 750 cc.; January 27, 2000 cc.; January 28, 0.1 cc., 2000 cc.; February 1, 0.25 cc., 2000 cc.; February 2, 2500 cc.; February 3, 0.5 cc., 1750 cc.; February 4, 2000 cc.; February 5, 0.75 cc., 1500 cc.; February 6, 2000 cc.; February 7, 1500 cc.; February 8, 0.75 cc., 1250 cc.; and February 9, 1500 cc. The 1 cc. injection of pitressin tannate in oil made her ill for 36 hours with nausea, shakiness, and "pressure in the head." There were no reactions or unpleasant symptoms after the other injections.

CASE 8. Female started treatment at age of five, but the polyuria and polydipsia began spontaneously at age of three. Nocturia occurred as often as one-half to one hour and the 24-hour urine averaged 4000 to 6000 cc. A daily injection of posterior pituitary solution gave partial relief. Pitressin tannate in oil was given hypodermically in 1-cc. doses every other day. The 24-hour urine then averaged 1500 cc. in amount for each of the two days. When the effect of the treatment began to wear off, the patient felt nervous and anxious.

CASE 9. Male, aged 46, 24-hour urine specimens contained 3500 cc. and 3870 cc. He was given some ampules of pitressin tannate in oil, and he took one daily by injection for eight days. He reported on the fifth day, saying that he urinated every half hour in small amounts. He had urinated every 15 minutes on the sixth day. On the seventh day he drank one glass of water. On the eighth day he called and said that he had urinated practically none during the

last 24 hours. Treatment was discontinued and in 48 hours he was urinating quite freely again. *Diagnosis:* Hysteria. He admitted that he drank a lot of water because he thought it made him feel better to urinate a lot. During the first four days of treatment he felt worse, whereas a case of diabetes insipidus would have felt better. He noticed a greater effect on pitressin tannate in oil during the first 24 hours than he did from posterior pituitary solution. On the last two days there was oliguria with water intoxication, and he felt "terrible" with headache, weakness, and a "stuffed feeling." This case was included to show the effect of an overdose of the antidiuretic hormone.

**Discussion**—Six cases of diabetes insipidus were treated with the antidiuretic hormone with symptomatic improvement and restoration of the water balance. A patient with hysteria who had the habit of drinking water excessively was not benefited, and oliguria and the symptoms of water intoxication were produced. When the hormone was administered hypodermically, the best results were obtained. Intranasal use was satisfactory, however, when it did not produce nasal irritation or allergic rhinitis. Some benefit was obtained from sublingual absorption. *Pitressin tannate in oil* was the preparation of choice for hypodermic use. *Desiccated posterior pituitary powder* was more practical for intranasal use. This latter method was the most economical.

Three of the cases were hereditary, coming from a family having five known members with diabetes insipidus. Two of these cases were identical twins, both having the disease. One case occurred after shock caused by an earthquake, while another was caused by shock and injury from an automobile accident. No apparent cause was found in two cases. Measles encephalitis was responsible for temporary diabetes insipidus in a boy.

The pitressin prevented the water loss from the kidneys. It also holds the water within the body cells. Therefore, the pa-

tients usually gained weight when treatment was started.

Only the pitressin preparations can safely be used during pregnancy as the others contain the oxytocic factor that causes uterine contractions and may cause an abortion. Two pregnant women did not abort in spite of using posterior pituitary powder intranasally and injections of 1 cc. of posterior pituitary solution.

Pitressin tannate in oil was much more effective than pitressin aqueous, unit per unit. In fact, the five-unit ampules of pitressin tannate in oil were more effective than the 20-unit ampules of aqueous pitressin or the 1 cc. ampules of posterior pituitary solution. In five cases a single injection of pitressin tannate in oil produced less excretion of urine in the following 24 hours than any other preparation given in one injection. The duration of the effect was much longer with pitressin tannate in oil, being from 48 to 72 hours. A mild case was satisfactorily treated by an injection every other day. A severe case requiring three injections of 1 cc. of posterior pituitary solution per day was satisfactorily controlled by a single daily injection of 1 cc. of pitressin tannate in oil. Patients frequently took their daily injection of posterior pituitary solution in the evening or late afternoon to prevent nocturia. If they were going some place during the day, they took it in the morning so as to avoid frequent urination while away from home. With pitressin tannate in oil the injection could be taken regularly at any specified time of the day as the effect was practically continuous. The undesirable side effects, such as pallor, palpitation, bowel cramps, nervousness, etc., caused by the larger injections of posterior pituitary solution were reduced to a minimum and not noticed by

the patients taking pitressin tannate in oil.

There was no evidence of the formation of habit or tolerance of any of the antidiuretic preparations. Neither was there a cumulation of effect beyond the period of absorption from the local area. Pitressin tannate in oil had a greater effect on the second day when injections were given daily, because absorption was still taking place from the first site of injection.

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## THE THYROID

**Goiter in Children**—Reports<sup>25</sup> of an incidence of 50 per cent of children in certain districts as goitrous and a 90 per cent goitrous population in an industrial school are discussed. No evidence of mental deficiency or cretinism was found, nor was there any evidence of dietary iodine deficiency, and iodine administration produced no dramatic results. The conclusion drawn, therefore, was that the goiters were hypertrophic and in all probability physiological.

What constitutes thyroid enlargement appears to be based upon individual standards, thus goiter surveys lack a common standard of measurements of the enlarged gland. In institutions it has been found that the incidence will vary from 5 per cent in one year to 51 per cent in the following year if a change of medical officer has occurred. Turton is quoted as stating that the incidence of childhood goiter was only of value as evidence of prevailing thyroid disease when considered in relation to the prevalence of cretinism, the proportion of sexes affected, and the incidence of goiter in the adult populations.

Many childhood goiters disappeared spontaneously, as for example in Derbyshire, 48 per cent of the childhood goiters resolved without therapy. There are at least two phases of thyroid activity which

are not synonymous—secretion and colloid storage. It is a mistake to regard the thyroid activity as being concerned solely with the metabolism of iodine. The only type of endemic goiter which is amenable to iodine treatment is the diffuse colloid or vesicular goiter. Secretory tissue is entirely absent in this goiter; the hypertrophic is usually a physiological enlargement of the thyroid gland, occurring between the ages of 9 and 16 years; it can have no relation to iodine deficiency because it is secretory in type and true hypertrophy. The colloid goiter is found in cretins, in cretinoid infants, and in the newborn of goitrous mothers. The major incidence is between 11 and 14 years, and it is not found in a progressive stage after 18 years of age. Imbalance of calcium and phosphorus, as well as iodine deficiency, play a rôle in the etiology. That closer attention should be given to the therapy of children with goiter is clearly set forth in the concluding statements of the article when it is stated: "For these reasons there is no justification for the promiscuous administration of iodine to school children merely because of the prevalence of thyroid enlargements. The hypertrophic type will not be benefited unless all of the factors operating in its causation are corrected, and it has been shown that an excess of iodine may be one of them. Secondary Grave's disease is too often a misapplication of iodine therapy to hypertrophy of the thyroid gland, especially in adolescents, and the continuous use of iodine can do nothing but harm to the critically balanced hypertrophic goiter of the young."

**Congenital Myxedema Without Mental Retardation**—Mussio Fournier and Cervino<sup>26</sup> cite the fact that infantile myxedema, particularly if congenital, is attended by both physical and mental underdevelopment. The mental under-

development is likely to be accompanied by certain psychic and pathological disturbance. In an infant under 10 months of age, the mental deficiency is usually betrayed by such signs as lack of the sucking reflex, delayed aptitude for holding the head erect, fixing the eyes, recognizing parents and relatives, grasping and playing with objects, turning over, sitting unaided, and standing with aid.

As the age of the child advances, more reliable methods of evaluating mental development are available as the assimilation of language, school progress, mental tests, and social habits. Thyroid insufficiency in these ages is consistently manifested as a reduction of general activity, changes in emotional balance, behavior, and the power of concentration. All the aforementioned are manifested in degree and in proportion to the degree of thyroid hypofunction. The authors have not found in the literature any single instance of infantile myxedema without marked mental deteriorations.

Their report of congenital myxedema without mental deterioration concerns a male, age  $10\frac{2}{3}$  years. The major complaints were: Underdevelopment, obesity, anorexia, constipation, increased thirst and perspiration, headache, depression, night terrors, apathy, procrastination, sensitiveness to cold, and delayed dentition. Growth retardation began at age three years. The headaches, lasting from 24 to 48 hours, began at age five years and are accompanied by photophobia and conjunctival congestion.

Mental development was normal throughout infancy, although apathy was noted at age three years, but at age  $10\frac{2}{3}$  years his intellect is normal.

The patient showed a 10.5-inch height deficit and a relative obesity and infantile proportions between the upper and lower measurements. The skin was dry, coarse, thick, infiltrated, and sallow. There was

slight cervical and dorsal lanugous growth. Muscular development was very good. Lordosis was present in the lumbar region. The head was relatively large. There was puffiness of the face and the nose was saddle shaped. The lips were swollen and the tongue was thick and large. Dentition was delayed, the six-year lower molars were absent and the upper molars were just erupting, and deciduous teeth were present. The neck was short and thick, and the thyroid was not palpable. The abdomen was protuberant. The genitalia were normal. The intelligence quotient was 1.13.

**Laboratory Findings**—Blood cholesterol, 265 mg. per cent; blood sugar, 115 mg. per cent. Secondary anemia.

**Roentgenography**—Dolicocephaly with thinning at the bregma. The sella turcica was enlarged. The sphenoidal and frontal sinuses were lacking. There was an osseous retardation of the long bones; the osseous age was four years.

**Therapy**—The patient has received *thyroid* for two years and has shown striking physical improvement. A height gain of 6.2 inches and a change of proportion from infantile to normal has been observed. The mental age and chronological age are practically equal.

The authors believe that the inception of the thyroid deficiency began before the age of three years, the period at which diminished activity appeared. They state that "practically all thyroid deficiencies are congenital which begin before the age of five, whatever the time of onset between birth and the fifth year."

At age one year, the child had one tooth. Only the emotional activity of the mental make-up of the patient was disturbed; other functions remained normal.

The rarity of such a finding as myxedema is the reason stated for reporting it in a separate paper because the oc-

currence of a more or less marked degree of failure of the thyroid will undoubtedly have an influence on growth and on mental development.

**Hyperthyroidism Treated by Estrogens**—The basis for the use of the estrogens in treating overfunction of the thyroid<sup>27</sup> is founded on the findings that the rat thyroid develops an inactive phase and colloid degeneration. The other result of estrogen injection to rats is depression of anterior pituitary function; this results in diminished production of the thyrotropic factor which is the normal stimulant of thyroid function.

The first case report is that of a female age 25 who had had three operations for hyperthyroidism: bilateral ligation of the thyroid vessels, right lobe resection two months later, and a third stage operation two months later. Nine months later acute symptoms of hyperthyroidism were present. Blood estrogen value was found to be negative and she was administered 2000 R.U. of *Pro-gynon B* weekly. Improvement, weight gain, diminished pulse, general improved feeling of well being were noted in three weeks and the injections were increased to twice weekly. The therapy was maintained for nearly three months as pre-operative management and *thyroidectomy* was performed at this time. The section of the thyroid removed at operation showed a marked accumulation of colloid in the acini, the gross histological picture being very similar to the rat thyroid treated with estrogens. The significance of this observation is increased because it was possible to compare this section with one from the patient's thyroid removed four years previously. In the 1936 gland there is much more uniform distribution of the colloid in the acini and the lining cells are cuboidal rather than the tall columnar seen in the earlier (1932) gland. There was



scarcely any hyperplastic area to be seen, in contrast to the picture in the gland in 1932, which showed many large areas of intense hyperplasia.

Three more cases of hyperthyroidism, two females and one male, were administered estrogens. One female had had two thyroid operations and the other x-ray therapy. The former was not considered as being benefited by therapy. The failure was in part due to unfavorable economic and domestic situation; further there was no evidence of blood estrogen deficiency in the patient and menorrhagia had been a consistent state all her life.

The other three patients treated were considered to have been improved by estrogen therapy. The dosage varied from 4000 to 30,000 R.U. of Progynon B weekly.

The use of estrogens in the treatment of hyperthyroidism has been undertaken in numerous studies. There have been no consistency in the results obtained with estrogens in hyperthyroidism. The authors do not advance it as a cure for hyperthyroidism but only as a therapeutic agent in preoperative management of hyperthyroidism in individuals who fail to respond to the usual management.

They very pointedly state that in deficiency endocrine disorders "cures" are only obtained so long as the deficiency syndrome is corrected by maintenance of therapy.

**Thyrotoxicosis Treated with Thiourea**—Himsworth<sup>28</sup> refers to the work of Astwood in the study of the beneficial effects of thiourea and thiouracil in cases of thyrotoxicosis. Astwood found that thiourea in doses of 1 to 2 Gm. daily or thiouracil in doses of 0.2 to 1 Gm. daily, administered for a period of a few weeks, would cause the disappearance of the thyrotoxic symptoms. The patient's condition improved to the extent that his

normal activities could be resumed and control of the thyrotoxic state was maintained as long as the therapy was continued. The effects of the therapy are not observed for one or two weeks. The initial effect from the administration of these compounds is a decrease in the pulse rate and, as therapy is maintained, the pulse rate reaches normal. The thyrotoxic symptoms abate, the weight increases, the basal metabolic rate falls, and the blood cholesterol rises. To date there have been numerous studies of a limited group of thyrotoxic patients treated with *thiouria* and *thiouracil*, and no evidence of toxicity has been recorded. The possibility of latent toxic effects is of great concern because so far it has been necessary to administer these agents continuously to cases of thyrotoxicosis. Discontinuance of therapy results in the re-appearance of the thyrotoxicosis.

Thiourea and thiouracil have been referred to as antithyroid agents. It is unlikely that the prevention of thyroxine synthesis is an all-or-nothing reaction, so a relation may be assumed between the dose of antithyroid substance and degree of hypothyroidism produced. It seems advisable, therefore, that in using the substance clinically to reduce hyperthyroidism close attention should be paid to dosage, with the aim of decreasing the synthesis of thyroxine to a normal level, but not below, so that there is no indirect effect in increasing thyroid hyperplasia. If some such balance cannot be achieved, then the question of the ultimate effect of the treatment on the thyroid gland may become very important. Moreover, the possibility of nonthyroid effects of administration of thiourea must not be lost sight of, especially if the effect of the substance on the thyroid lies in preventing enzymic action.

While thiourea and related compounds appear to be of great potential impor-



tance as therapeutic agents, the effects of prolonged treatment will require careful study before the new technic can be accepted without qualification. These substances produce in experimental animals a hyperplasia of the thyroid gland and hypothyroidism. Williams and Bissell treated nine hyperthyroid patients with thiouracil; during the first three weeks 1.0 to 1.2 Gm. (15 to 18 gr.) were administered and in the second two weeks the dosage was gradually reduced. These observers found that the signs of thyrotoxicosis, clinical and laboratory, disappeared in from three to seven weeks after beginning thiouracil therapy. In six of their patients the thyroid gland progressively diminished in size and in two patients the thyroid gland became practically normal in size. The only untoward effects observed were in the two patients who developed a slight transient edema of the legs in association with a minor increase in the serum chloride and diminished  $\text{CO}_2$  combining power of the blood.

Himsworth studied the effects of administering 1 Gm. (15 gr.) of thiourea three times a day to six cases of severe thyrotoxicosis. A typical case report is presented.

The patient, a male, age 34 years, had had thyrotoxicosis for two years and had received iodine during this period. An acute respiratory infection was followed by an acute thyrotoxic state characterized by weight loss, irritability and nervousness, fatigue and weakness, sweating, palpitation, tremors, sleeplessness, diarrhea. On admission he was tense, overenergized, and his whole body was flushed and bedewed with sweat.

The eyes were staring, upper lid retraction and protrusion of the eyeballs were present. The pulse rate was 150. The thyroid gland was of firm consistency (characteristic of prolonged iodine therapy) and showed a moderate diffuse enlargement.

The general condition of the patient was so severe that 4-hourly *morphine therapy* (liq. morph. hydrochloride, 15 minims) was adminis-

tered in preference to intensive iodine therapy. During the eight-day period of this therapy two B.M.R.'s were made with results of plus 81 per cent and plus 82 per cent. On the ninth day the morphine was discontinued and the administration of *thiourea*, 1 Gm. (15 gr.), three times a day, was begun. On the eleventh day of this therapy the initial significant decline in the waking and sleeping pulse rate was observed. The pulse rate continued to decrease and on the eighteenth day it had reached normal and continued so. On the fifteenth day the B.M.R. rate was plus 34 and on the thirty-first day the B.M.R. was plus 21. He had gained 9 pounds in weight on the thirty-third day. The blood cholesterol had risen from 110 mg. to 225 mg. per 100 cc. and at this period there was no suggestion of his being a case of thyrotoxicosis. The staring eyes and lid retraction and conjunctival injection had disappeared. The protrusion of the eyeball had not diminished to any degree. The goiter was softer, but not diminished in size; in fact, neck measurement showed a slight increase in size.

The results in the other milder case of hyperthyroidism were similar to the dramatic results observed in this highly toxic case. In the other case the pulse rate decline was more gradual. One case required thyroidectomy because of pressure on the trachea. Thiourea was found to be an excellent preoperative agent in this case. The thyroid tissue removed from this patient treated with thiourea showed hyperplasia and the acini were practically free from colloid.

The two disadvantages observed by Himsworth were the nauseating taste of the thiourea and the occasional vomiting experienced at the beginning of therapy, and the sweet odor the drug imparts to the breath. No elevation of blood urea was observed nor was agranulocytosis found.

The mode of action of thiourea is discussed by Himsworth. The use of thiourea and thiouracil is an extension of the finding by the Mackenzies that the sulfaguanidines when administered in toxic doses to rats produce goiter. The

thyroid tissue of the rat goiter showed hyperplasia and loss of colloid. Richter then showed that thiourea and thiouracil, sulfur compounds as are the sulfaguani-  
dines, also produce the same gross and histological effect on the thyroid. The histological picture produced by the sulfur compounds resembles the thyroid tissue picture of human thyrotoxicosis; however, the experimental animal shows clinical evidence of hypothyroidism. The contradictory clinical picture can be explained by the studies of Marine, who showed this picture in experimental animals does not necessarily indicate hyperthyroidism and is explained on the basis that it is an effect resulting from the thyroid being stimulated by the body needs to offset a deficiency state of the thyroid or an iodine deficiency state. The production of more thyrotropic factor does not correct the disorder in the latter; only iodine administration will revert the histological picture to normal. The iodine is required for the production of the thyroid hormone and the excessive stimulation of the thyroid in the absence of iodine results in hyperplasia and loss of colloid. On the basis of reasoning the explanation could be advanced that thiourea and thiouracil neutralized the action of thyroxine on the body tissues, but this is disproved by the fact that in normal animals the effect of the administration of thyroxine is not neutralized by the simultaneous administration of thiourea. Williams and Bissell have shown that the simultaneous administration of thiouracil does not prevent an elevation of B.M.R. produced by the administration of desiccated thyroid to human myxedema. The administration of iodine to animals does not alter the thyroid histological picture of the thiourea treated animals. Since the hyperplasia does not occur in hypophysectomized rats treated with thiourea it

appears that excessive secretion of thyrotropic hormone of the anterior pituitary gland is produced by the administration of thiourea. Further analysis of the action of the anterior pituitary thyrotropic hormone on the thyroid gland brings the suggestion that thiourea prevents the synthesis of the thyroid hormone. Additional proof for this suggestion is provided in the finding that the colloid in the thyroid gland of animals treated with thiourea is devoid of iodine.

The ultimate effect of thiourea on the thyroid is projected as follows: The hyperplasia will ultimately be succeeded by atrophy and destruction of the source of the thyroid hormone. That atrophy ultimately succeeds this hypofunctional form of thyroid hyperplasia has been demonstrated by Marine.

**Summary**—The claims of Astwood regarding the strikingly beneficial effect of thiourea on cases of thyrotoxicosis have been confirmed in six cases, so far as the initial effect of the drug is concerned.

The evidence at present available indicates that thiourea acts by interfering with the synthesis of the thyroid hormone.

**Editor's Note**—Thiourea and thiouracil are at present not available except for clinical research. These substances are not the only ones which have shown antithyroid activity. Astwood has shown that certain aniline derivatives, among which are the sulfonamides, p-, m-, o-aminobenzoic acids, possess antithyroid activity. Thus, a new approach to the problem of controlling excessive endocrine function by chemical products has been added. Whenever a foreign chemical is introduced into the body to control an important physiological function and particularly an endocrinous function of the anterior pituitary, adrenal cortex, or the thyroid, extreme caution is war-

ranted before its continuous use is advisable.

**Thyroid Substances in Patients with Obesity**—Kall<sup>29</sup> states that prolonged medication or overdosage with thyroid substance administered for therapeutic purposes may cause the signs and symptoms of toxicity (hyperthyroidism), as palpitation, nervousness, tremor, diarrhea, weakness, and diaphoresis. Attention is called to the various reports which state that in human subjects receiving thyroid therapy, there has occurred acute dilatation of the heart, angina, left heart failure, cardiac involvement, such as is seen in Addison's disease, and auricular fibrillation.

Thyroid substance in conjunction with low caloric diets have been used to produce weight loss in obese individuals.

Two groups of obese patients were studied. Each was on a submaintenance diet.

There were 469 patients in the first group; 169 were given thyroglobulin (Proloid); 100 Parke-Davis thyroid; 100 Armour's thyroid; 100 were given placebos. Each thyroid preparation was given in doses of 0.065 Gm. (1 gr.) three times a day for two to 32 weeks; the drug was discontinued when toxic symptoms appeared.

The second group of 45 obese patients were on a submaintenance diet for four weeks, were divided into five subgroups, and were given thyroglobulin, Parke-Davis thyroid, and Armour's thyroid, 0.065 Gm. (1 gr.) three times a day for four weeks.

The thyroid substances used in the dosages already mentioned were without significant effect on the cardiac rate. None of the thyroid substances caused a change in either systolic or diastolic blood pressure. With the exception of palpitation (18 to 20 per cent), relatively few toxic reactions were experienced; no dif-

ference was observed in this respect between the various thyroid substances. Increased cardiac rate (over 100 beats per minute), however, appeared to be a more frequent observation in patients receiving Parke-Davis' or Armour's thyroid than in those given thyroglobulin.

These substances were administered in different time-relationships to each other in order to determine if the results produced by a given thyroid substance could be duplicated. A low-caloric diet supplemented by thyroid substances, regardless of the order of rotation, is followed by a loss of weight ranging from 19 to 46.2 pounds per patient over a period of 18 weeks. In general, the pulse rate was accelerated in over 90 per cent of the patients by each of the thyroid substances used. Each of the thyroid substances caused increase in basal metabolic rate to the same degree.

**Discussion**—Although the various thyroid substances used in this study were shown to have exerted different calorogenic effects, the action of each on pulse rate was not dissimilar.

In so far as the study of weight loss in the obese patient is concerned, no further comment need be made other than that a definite weight loss was observed. In a previous publication from their clinical, it was concluded that *desiccated thyroid* alone, or in combination with *amphetamine (benzedrine) sulfate* failed to increase the rate of weight loss over that resulting from the submaintenance diet alone.

In general, toxic symptoms were not prominent except in the indicated instances. In another report it was pointed out that many of the symptoms, such as headaches, weakness, palpitation, and nervousness, were observed in a significant number of obese patients who were on low-caloric intake alone. The figures for toxic symptoms attributable to thy-

roid reported here, therefore, may be too high.

**Summary and Conclusions**—1. Thyroid substances administered in doses of 180 mg. (3 gr.) daily produced no change in either systolic or diastolic blood pressure in obese patients.

2. The administration of thyroid substances resulted in cardiac acceleration, but the effect of the various preparations used on the pulse rate was not dissimilar.

3. Relatively few toxic manifestations were noted; palpitation was the most common.

4. The administration of thyroid substances resulted in an increase in the basal metabolic rate. *Parke-Davis thyroid* appeared to be the most calorogenic, *Armour's thyroid* the least, and *thyroglobulin* occupied an intermediary position.

**Tolerance to Oral Thyroid and Reaction to Intravenous Thyroxine in Subjects without Myxedema**—This paper<sup>30</sup> describes the responses of various nonmyxedematous subjects to thyroid medication.

These patients repeatedly exhibited an ability to tolerate 0.324 Gm. (5 gr.) or more of *thyroid* without manifesting a persistent elevation of the B.M.R. or the pulse rate. One patient had received between 0.194 and 0.454 Gm. (3 and 7 gr.) of thyroid for a period of eight years. A gradual trend of the metabolism to a lower level had occurred as thyroid therapy was maintained and discontinuance of thyroid produced a drop in the B.M.R. below current level, though later it tended to rise spontaneously. The patient experienced weight gain and weakness within two or three days following interruption of therapy. This, in the authors' opinion, "could hardly have been due to complete exhaustion of thyroid effect." This patient could tolerate 0.454 Gm. (7 gr.) of thyroid without

subjective disturbance and with a B.M.R. of minus 21 per cent.

Another patient tolerated 0.39 Gm. (6 gr.) of thyroid daily without effect on the B.M.R. or pulse rate and no change was noted in the B.M.R. or pulse rate when thyroid was discontinued. Weight gain occurred when the thyroid was discontinued.

The two patients who exhibited this indifference to the effect of orally administered thyroid reacted markedly to *intravenous thyroxine*. B.M.R. and pulse rose, nervousness and tachycardia developed, and weight loss occurred.

Certain subjects showed an initial rise in the B.M.R. to 0.194 Gm. (3 gr.) of thyroid, but subsequently the B.M.R. fell to the initial level. It was necessary to give this group of patients 0.324 Gm. (5 gr.) of thyroid before the B.M.R. could be elevated to normal, and slight subjective phenomena, slight pulse elevation, weight loss, and nervousness were obtained. This group of patients showed a response to intravenous thyroxine.

Nineteen patients with clinical evidence of hypometabolism, including four cases of obesity and four cases of hypothyroidism, failed to show significant changes in the B.M.R. from the administration of 0.065 to 0.26 Gm. (1 to 4 gr.) of thyroid orally administered, 0.065 Gm. (1 gr.) of thyroid administered for from eight to 40 months in hypothyroids whose B.M.R.'s ranged from minus 25 per cent to minus 12 per cent, failed to produce any material change in the B.M.R. Increasing the dosage of thyroid above 0.065 Gm. (1 gr.) daily brought about untoward reaction in many of this group of hypometabolic patients. The B.M.R.'s in this group of patients were definitely in the levels observed in hypothyroidism; their most common symptoms were obesity, dry skin, alo-

pecia, somnolence, and menorrhagia. All but one of the patients were females.

Thyroid medication was without much beneficial subjective or objective effect in the majority of these patients. A few favorable responses were obtained, as weight control was more easily accomplished and energy output improved. Many patients voluntarily discontinued thyroid therapy because of its failure to be beneficial. This group of patients presented no deleterious effects from the therapy but differ sharply from patients with true myxedema, who consistently exhibit both subjective and objective improvement even on small doses of thyroid.

Prolonged administration of oral thyroid to many patients effected no change in their clinical state; occasionally some of these patients were shown to have mild myxedema. Many patients originally selected as eligible for this group developed unpleasant subjective reactions, such as palpitation, so promptly that they discontinued therapy. Clinically, this group corresponded to the former, and in the 12 patients who maintained therapy for two or more months, 0.065 to 0.13 Gm. (1 or 2 gr.) thyroid daily in most instances, an elevation in the B.M.R. occurred to low normal and in three patients it rose to a positive normal value.

Six patients were administered intravenous thyroxine. In nonmyxedematous subjects, more than 0.3 mg. of thyroxine daily was necessary to raise the B.M.R. and that 1.0 mg. of thyroxine daily was required to increase the B.M.R. to plus 25 or plus 30 per cent. These patients were about only one-third as responsive to thyroxine as the true myxedema case, since 0.2 to 0.3 mg. of thyroxine will produce a plus 25 per cent or plus 30 per cent rise in B.M.R. in myxedema cases. In total iodo equivalents, thyroxine was

much more effective than thyroid. One milligram of thyroxine contains the same total amount of iodine as 0.29 to 0.325 Gm. (4.5 or 5 gr.) of thyroid. Only 0.3 of the iodine in thyroid is thyroxine iodine. Six grains of thyroid contain about 0.72 mg. of total iodine, contains 0.22 mg. of thyroxine iodine and therefore 0.33 mg. thyroxine.

The authors state a good many patients can tolerate 0.13 to 0.194 Gm. (2 or 3 gr.) thyroid orally daily, and some who can tolerate 0.39 to 0.454 Gm. (6 or 7 gr.), without effect on the B.M.R. The B.M.R. of myxedematous patients react with a 25 to 30 per cent increase of the B.M.R. when thyroid, 0.194 Gm. (3 gr.) daily, is given. Three possible interpretations are considered: (1) Improper absorption of the administered thyroid; (2) tissue insensitivity to the administered thyroid; (3) inactivation, destruction, or storage of the administered thyroid. Grounds for eliminating the first two possibilities are presented and only the third factor holds reasonable possibilities of explaining the observed negative response of the patient to oral thyroid and intravenous thyroxine.

Under oral thyroid administration gradual absorption of the hormone occurs; intravenous thyroxine therapy allows concentration of hormone effect. Accordingly, these patients while inactive to oral therapy do respond better to thyroxine but still are less sensitive to thyroxine than the myxedema case. The inactivation hypothesis is further postulated on the extraordinary avidity of the thyroid gland for iodine and the low iodine content of the serum in these patients is an additional suggestion concerning the disposition of the introduced iodine containing hormone. In myxedema patients there is little or no functioning thyroid tissue; the storage or inactivity depot does not exist. This explanation

they state needs the support of research and experimental work and at present their views are only a tentative hypothesis built from the facts as they are now known.

**Conclusions** — 1. Certain nonmyxedematous subjects can tolerate as much as 0.39 Gm. (6 gr.) of dried thyroid daily for long periods, without effect on the B.M.R. or on the pulse rate. Many others can tolerate as much as 0.194 to 0.26 Gm. (3 or 4 gr.) daily without effect on the B.M.R.

2. These subjects respond to thyroxine intravenously, but require much larger doses than do myxedematous subjects to produce a comparable rise in the B.M.R.

3. This behavior is very different from the absence of tolerance and the acute sensitivity to thyroid and to thyroxine of the patient with myxedema.

4. It is suggested as a working hypothesis that this difference of behavior can best be explained by assuming that the nonmyxedematous subject possesses the ability, wanting in the patient with myxedema, to inactivate thyroid substance and intravenous thyroxine.

**Thyroidal Action of Synthetic Thyroprotein**—Reineke and Turner<sup>31</sup> report the finding of a synthetic thyroprotein which has several times the thyroidal activity of desiccated thyroid.

They refer to the early work of Bauman, Hutchinson, and Oswald in the identification of thyroglobulin as an iodoprotein and the studies of and production of iodoproteins. The clinical studies of these products produced negative results; this the authors consider to be due to their "failure to establish the optimum conditions for the desired reactions to take place."

Research in this field was neglected for about 20 years until in 1934 Abelin and his co-worker produced an acid insoluble precipitate by first hydrolyzing

with alkali the iodinated protein. The preparation contained 26 per cent of iodine and was designated homothyroxine. In 1896 Hutchinson had increased the iodine content of thyroid colloid without affecting any increase in thyroid activity of this preparation. The intervening events of importance in thyroid chemistry was in 1915 when Kendall identified thyroxine as the active principle of the thyroid gland and the synthesis of thyroxine by Harrington in 1926.

In 1928 Galler and Lerman prepared an active thyroid preparation by the iodination of blood serum, using the same procedure of obtaining an acid-insoluble product, and in 1939 reported favorable clinical effect obtained in myxedematous patients and thyroidectomized animals with iodinated serum protein as well as its acid-insoluble degradation products.

In 1939 Ludwig and von Mutzenbacher announced the isolation of crystalline thyroxine from barium hydroxide hydrolysates of iodoproteins. Harrington and Rivers confirmed this finding in 1939. Physiological assays of the iodoproteins before hydroleptis and concentration of the active principle had shown either negative results or a relatively low order of potency.

Reineke and Turner undertook a research study to obtain a product by iodination and subsequent treatment of the protein with high activity, if possible, without further digestion and concentration of the thyroidal substance. They report the finding of such a preparation together with biological tests of its thyroid activity.

The biological tests used in the earlier work were stimulation of increased oxygen consumption of guinea pigs and by stimulation of tadpole metamorphosis (Gudernatsch—1913). After a series of consistent findings in the two tests the tadpole metamorphosis test was used ex-



clusively. The test adopted was the induction of ovulation in female frogs, and artificial insemination and incubation of the eggs and the maintenance of a stock of tadpoles for this work during most of a year. Ingestion of thyroxine or of the active iodinated protein solutions would stimulate rapid metamorphosis, the percentage decrease in body length of the tadpole varying as the logarithm of the dosage. A negative response was observed with diiodotyrosine or potassium iodide.

It was found that there was an optimal pH for the preparation which was between 6.8 and 8, and that the introduction of iodine above 2 atoms per molecule of tyrosine led to significant loss in thyroidal activity.

Comparative assays of the active iodinated protein and U.S.P. thyroid powder in guinea pigs indicated the former was more active per unit of weight than the U.S.P. thyroid when tested by the same mode of administration.

It was further found that by increasing the temperature at which the iodination of the protein was effected a marked increase in activity was obtained and a maximal effect was obtained at 70° C. Repeated assays of the 70° C. preparation revealed that a four-fold increase in thyroid activity was obtained over that of the products made up at the usual temperature of 38° C.

The administration of this artificial thyroprotein has been found to be effective therapy in preventing cretinism in thyroidectomized goats and when administered in sufficient quantity will stimulate growth approaching the normal. When administered to cows and goats this will induce an increase in milk production similar in every way to that observed when desiccated thyroid or thyroxine are administered.

From 100 Gm. of this product they were able to obtain 424 mg. of crystalline thyroxine which is more than three times the analytical value for thyroxine which is normally obtained with thyroid powder containing 0.2 per cent iodine. By biological assay the crude iodinated protein preparations have shown at least four times the thyroid activity of a commercial thyroid powder with which they were compared.

The authors conclude their investigations of the thyroid activity and qualities of their prepared iodinated protein indicate that it has many times the activities of thyroid powder, as judged either by its biologic assay or by the actual yield of crystalline thyroxine which can be recovered from it. The iodinated protein is active when given orally, and in experimental animals it has also been found to be highly active by subcutaneous injections.

The preparations exert an effect that is indistinguishable, qualitatively, from that of thyroxine or thyroid substance.

Protein sensitization has not been observed in experimental animals receiving daily injections of iodinated proteins for several weeks.

**Perithyroiditis** - DeCourcy<sup>32</sup> is of the opinion that Riedel's struma is the result of a previous perithyroiditis. The fibrous growth characteristic of the disease begins outside rather than within the thyroid gland; partial constriction of the vessels entering the gland occurs and subsequent fibrous tissue formation follows. DeCourcy therefore considers Riedel's struma primarily a vascular disease. The prevention of Riedel's struma therefore resolves itself in proper management of the case of perithyroiditis. Concerning this condition there is a scarcity of information.

The clinical events which he has observed in cases of perithyroiditis are:



The presence of a diffusely enlarged thyroid (from two to three times the normal size) and a history of acute illness with fever, chilliness, pain, and tenderness in the thyroid gland. The tenderness in the thyroid persists for as much as eight weeks. The temperature and blood count at this period are normal. "These symptoms are typical and in my opinion characterize the entity perithyroiditis." The B.M.R.'s are normal or slightly elevated. The patients further complain of the continued tightness of the throat, the persistent enlargement of hardened consistency, and nervousness.

A recent case presented an interesting course of events. For a period of eight weeks the temperature persisted, range 99° to 101.6° F. Signs of suppuration were absent. **Chemotherapy** was ineffective. **Radiation therapy** brought about a normal temperature and disappearance of the tenderness but the hard swollen thyroid gland persisted. **Surgery** was refused. Slight nervousness and tightness around the throat have persisted.

On the basis of the author's observations it seems likely that in diagnosing acute nonsuppurating thyroiditis observers have been witnessing the onset of Riedel's struma. None of the glands affected with this disease suppurate. It has been his experience that suppurative thyroiditis develops within a comparatively short time and that it is usually accompanied by cellulitis of the neck. In contrast, early fibrosis was the rule in the cases under discussion.

One must not overlook the fact that during the acute phase of perithyroiditis the febrile symptoms are so mild as to cause many of the patients to go untreated. Not infrequently the condition is diagnosed as grippe or cervical adenitis. The soreness disappears and the

patient leaves the physician's care only to seek a surgeon later.

In view of these findings the explanation which he offers is that primary perithyroiditis with the adherent edematous muscles and lymphangitis partially occludes the blood vessels entering the thyroid gland and causes the entity known as Riedel's struma. In brief, Riedel's struma is a vascular rather than a glandular disease.

Iodine does not seem to be a causative factor, because in a recent case of eight weeks' standing the patient had been given no iodine before the onset of the disease.

**Summary and Conclusions**—Perithyroiditis is a distinct entity with a definite train of symptoms and sequelae. Perithyroiditis is the etiologic factor in the formation of Riedel's struma. Additional evidence submitted tends to confirm the view that Riedel's struma is a vascular rather than a glandular condition.

**Carcinoma of the Parathyroid Gland**—Carcinoma of the parathyroid gland is rare and the authors<sup>33</sup> give a complete report on their case and the postmortem findings.

The patient had the typical clinical, laboratory, and x-ray findings diagnostic of hyperparathyroidism, diffuse fibrocystic disease of the bone, and calculi in both renal pelvises.

The removal of the tumor of the right parathyroid gland produced distinct relief from the subjective symptoms, normal serum calcium, and slight recalcification of bone. Five months later there was a recurrence of the pain in the bones. Seven months later hypercalcemia and hypophosphatemia were present and a hard nodule was noted in the region of the right lobe of the thyroid fixed to the right jugular and carotid artery. X-ray therapy of the area was instituted and

continued for eight months. The mass increased in size and the hyperparathyroid state progressed. The patient died 26 months after the original operation.

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## ENDOSCOPY

LOUIS H. CLERF, M.D.

## BRONCHOSCOPY

## Bronchospirometry

While the importance of bronchospirometry in the evaluation of patients with pulmonary disease has been generally admitted, it has not come into widespread use because it is generally considered that the procedure is highly technical and complicated and cannot be performed without the aid of a research laboratory. In discussing this, Steele<sup>1</sup> pointed out some of the problems that are met with and also offered a solution for these. He expressed the opinion that valuable clinical results can be obtained in any hospital or sanatorium by determining the

oxygen consumption of each lung separately by simply connecting an ordinary basal metabolism apparatus to each side of a double channelled soft rubber catheter which has been introduced into the tracheobronchial tree.

## Bronchoscopy in the Newborn

While bronchoscopy is seldom indicated in the treatment of diseases of the newborn, there are rare occasions when it is a life-saving procedure. Woodward and Waddell<sup>2</sup> reported their results in a series of cases and found that it is of value in atelectasis due to obstruction of the bronchi by thick secretions. While the procedure should not be undertaken

too lightly or too hastily, if properly sized bronchoscopes are employed, no ill effects will be observed.

The indications for bronchoscopy in the newborn are not clear cut and the decision, therefore, must be made in the individual case only after careful consideration by the pediatrician and the bronchoscopist. In view of its employment with safety, it would seem that the method could be utilized more frequently where the indications are definite and positive.

### Acute Laryngotracheobronchitis

While *bronchoscopy* and *tracheotomy* have commonly been accepted as a part of the treatment of acute laryngotracheobronchitis, Baum<sup>3</sup> pointed out that these do not always relieve the underlying pathological condition. Tracheotomy for the relief of dyspnea frequently has serious consequences, predisposes to lower respiratory difficulties, and should be avoided if prompt and adequate relief can be obtained without it. He found that the intravenous administration of *hypertonic human plasma* often will promptly reduce subglottic edema to the point of comfort and safety. *Humidified oxygen* is valuable for the relief of respiratory distress, and often gives necessary respite while other measures are in preparation or taking effect. *Convalescent human serum* is best to combat the infection in the respiratory mucous membranes.

While no statistical data are given, in Baum's experience the results of non-surgical treatment have been most encouraging and should be employed as promptly as possible. If they fail, surgical measures can be resorted to but these aids will be found equally effective and valuable as adjuncts to surgical treatment.

### Scleroma

Involvement of the upper and lower respiratory passages by scleroma is not commonly observed. Dixon<sup>4</sup> reported the case of a man, 65 years of age, who exhibited warty granulations attached to the nasal septum, thickened vocal cords, and a warty growth similar to that observed in the nose attached to the lateral wall of the trachea. The tracheal walls exhibited marked distortion. Microscopic studies of tissue removed from the nose and trachea were reported as rhinoscleroma. *Klebsiella rhinoscleromatis* was recovered from the tissue on blood agar. The patient received *roentgen therapy* and exhibited definite improvement. Later, however, difficulty in breathing occurred and it was necessary again to remove tissue both from the nose and the trachea. Although definite improvement has been observed from roentgen therapy, there has been a tendency for the granulomatous mass to recur slowly.

### Hemoptysis

Hemoptysis is a very common symptom and may occur in many different conditions. Parrish<sup>5</sup> divided these into two main groups, namely, lesions arising within the respiratory tract or lung structure and lesions arising outside the respiratory tract, which by growth or other means invade the respiratory tract. A third group might also be considered, namely, trauma, either direct or indirect, involving the respiratory tract or lung structure. While in many cases the cause and location of the bleeding can be readily determined, in others it may be found with difficulty or may not be discovered except at post mortem.

In the more obscure cases, bronchoscopic examination often is resorted to as a diagnostic aid. All available diagnostic measures should be carried out.

however, before bronchoscopy is performed since certain of these cases can be diagnosed by physical examination and roentgen study of the chest. In addition, careful blood studies should be done. Parrish agreed that a small hemorrhage is not a contraindication to bronchoscopy; in fact, a small amount of blood in the tracheobronchial tree at the time of examination may be of distinct aid in localizing the bleeding point. If the hemorrhage is great, however, bronchoscopy is of limited or often of no value since the quantity of blood interferes with a satisfactory view of the bronchi.

### Postoperative Pulmonary Complications

An analysis of the origin of postoperative pulmonary complications makes it appear that some are avoidable, while others are beyond the control of the surgeon or anesthetist. Eggers<sup>6</sup> emphasized certain preventive measures which should be observed. If, in spite of these, a complication threatens or develops active therapeutic measures should be promptly instituted. One of the most important is *removal of excessive secretions* in the pharynx and bronchial tree. If simple measures prove ineffective, it may be necessary to resort to *intratracheal suction* or *bronchoscopic aspiration*. If it is suspected that coarse particles of infected material have been aspirated, a *bronchoscopy* should be done immediately after operation. Bronchoscopy also is to be preferred if the entire bronchial tree is filled with secretion since it permits of complete aspiration of the larger bronchi.

### Bronchiectasis

Stacey<sup>7</sup> found that the oral administration of sulfonamides over a period of months failed to control acute infections or lessen the toxic symptoms in patients

with bronchiectasis, and in addition there developed an increasing intolerance to these drugs. He therefore developed a method of inhalation of nebulized solutions of *sulfonamides*. A 5 per cent solution of *sodium sulfathiazole* was employed, placing 1 cc. in a nebulizer which was connected by a rubber tube to an oxygen tank equipped with a flow meter. The patient held the nebulizer between the teeth and by slowly inhaling the nebulized solution was able to dispose of about 1 cc. of solution in 20 to 30 minutes. This method of treatment was found to be entirely free from local irritation and the amount of drug absorbed systemically was too small to be measurable. He expressed the opinion that there was secured distinct benefit in a small series of cases of bronchiectasis and that the method was worthy of further study.

In discussing bronchiectasis in children, Wishart<sup>8</sup> expressed the opinion that *bronchoscopic aspiration, injection of iodized oil* under general anesthesia, and *bronchography* have proved of unquestioned benefit in the study and treatment of this condition. During the past 13 years, 433 cases have been diagnosed as bronchiectasis and 1015 records of these cases have been studied. The iodized oil is introduced into the lung by means of bronchoscopy under general anesthesia. Bronchography has been done on patients under two years of age and suction on patients under one year of age without any complication.

These preliminary studies disclosed the cases in which major surgical treatment is contraindicated and also determined those in which the only known cure, namely, surgical extirpation of the diseased lung is suitable. *Bronchoscopy* provided the most effective form of treatment of the large group which does not require major surgical treatment. Bron-

chography permits early definite diagnosis of the disease and therefore affords the hope that further progress of a most devastating disease can be checked.

### Tuberculous Tracheobronchitis

In discussing the treatment of tuberculous lesions of the trachea and bronchi, Davies<sup>9</sup> found by reviewing the literature that there are many who believe local treatment of these lesions is useless, whereas others believe that it has definite value. Considerable question also exists as to the best plan of therapy, some advocating the employment of *cauterization by silver nitrate* or other agents, while others believe that all of these are harmful in that they produce excessive scarring and stenosis of the bronchus.

He believed that bronchoscopy itself is harmless in tuberculous patients with or without tracheobronchial lesions, provided proper technic is employed and that contraindications are respected. In a series of approximately 400 bronchoscopic examinations in 156 patients he has seen no evidence of harm in a single case. He prefers a 30 per cent solution of silver nitrate, believing that this does not increase the amount of scar tissue over that which would be normally laid down if the lesion healed spontaneously.

The following program is suggested as a tentative but reasonable basis for the treatment of patients with tuberculous tracheobronchitis, namely, complete bed rest in a sanatorium and a diet adequate in all essentials; relief of symptoms by a warm, humid atmosphere, adequate fluid intake, postural drainage, and the use of expectorants, antispasmodics, and barbiturates as necessary; persistent bronchoscopic cauterization of all accessible ulcerated lesions at bi-weekly intervals, preferably with a 30 per cent solution of silver nitrate; use of *collapse therapy* if the parenchymal

lesion by itself demands collapse or if a main or lobar bronchus is seriously obstructed and if the obstruction cannot be promptly relieved. If collapse is indicated, complete thoracoplasty is usually the procedure of choice. In a few exceptional cases, *lobectomy*, *pneumonectomy*, or *open cavity drainage* may be used when more conservative measures have failed.

The interest in tuberculous tracheobronchitis and the information secured by bronchoscopic investigation has suggested to many that routine bronchoscopic examination should be made on all patients admitted to sanatoriums. Others have a more conservative attitude and have limited bronchoscopic investigation only to cases amenable to collapse therapy. The accumulation of more clinical data pertaining to this subject has resulted in the acceptance of certain general indications for bronchoscopy in tuberculous patients. These are summarized as follows:

Intermittent or unexplained atelectasis; wheeze; persistent positive sputum which is inconsistent with the clinical and roentgenological course; marked variations in the daily sputum volume; unexplained hemoptysis; as a routine procedure prior to thoracoplasty; and, to determine the source of positive sputum in the absence of roentgenologically demonstrable parenchymal lesions.

It is believed by many that routine bronchoscopy is not necessary and offers little information over that obtained from the bronchoscopic examination of patients who have presented one or more of the above noted indications.

In a study of postbronchoscopic reactions, Radner<sup>10</sup> collected data on 183 bronchoscopic examinations made on patients with pulmonary tuberculosis. There were noted 18 cases of postbronchoscopic fever, which appeared to be of

little significance and in 26 there was a secondary rise in temperature appearing between the tenth and sixteenth bronchoscopic day and lasting two to three weeks. In 21 there was a minimal infiltrative spread as shown on roentgen films and in five the bronchoscopic examination was followed by atelectasis of a lobe or a lung. He suggested that patients subjected to bronchoscopy prior to thoracoplasty should have deferred any surgical intervention for at least three weeks and the interval between bronchoscopic examinations or treatment should not be less than six to eight weeks to allow for subsidence of any reaction resulting from previous treatment.

## ESOPHAGOSCOPY

### Cricopharyngeal Sphincter

Although much of the knowledge concerning the physiology of the cricopharyngeus has been obtained from endoscopic observations, these probably are inadequate to permit of exact conclusions. Only the presenting surface and not the entire sphincter is seen esophagoscopically. In addition, the presence of the esophagoscope might give rise to abnormal appearances and action. Templeton and Kredel<sup>11</sup> devised a roentgenologic technic which has made it possible to study the physiology of the cricopharyngeus by a totally different method. These newer observations, however, support the endoscopic opinion, that the cricopharyngeus possesses the function of localized contraction and is in every sense a true sphincter muscle.

### Cricopharyngeal Spasm

The term cricopharyngeal spasm often is used synonymously with functional dysphagia, spasmodic stenosis, globus hystericus, hysterical dysphagia, and esophageal neurosis. In discussing this condition, Clerf and Putney<sup>12</sup> found that

with present diagnostic aids it is difficult to demonstrate dysfunction of the cricopharyngeus muscle.

In the presence of disease of the cervical esophagus, as carcinoma or foreign body, and in chronic hypopharyngitis it is reasonable to assume that incoördination of the swallowing function does occur; however, it is not always possible to differentiate between this and the changes produced by the disease itself. Further, it cannot be ascertained whether reflex stimuli are producing increased involuntary tonic contractions (spasm) of the cricopharyngeus or there is lacking the necessary stimulus to relax the normally contracted sphincter. In addition the circular muscle fibers of the upper esophagus which are striated and receive practically the same innervation as the cricopharyngeus, have a related function and probably participate in the mechanism of incoördination of the upper esophageal constrictor. One, therefore, should consider in the differential diagnosis carcinoma, foreign body, pulsion diverticulum, congenital or acquired stenoses, chronic hypopharyngitis, chronic esophagitis, cardiospasm, disturbances of the thyroid gland, and a host of other conditions about the neck and upper mediastinum. Certain laryngeal disturbances also may give rise to indefinite symptoms referable to the swallowing act.

### Dysphagia

Displacement of the esophagus is not unusual in mediastinal neoplasms which do not have their origin in the esophagus. Because of the relative infrequency of symptoms referable to the esophagus in these cases, Hill and Vinson<sup>13</sup> studied a series of 50 cases of mediastinal tumor with reference to pressure on the trachea, bronchi, and esophagus. In 32, pressure on the air passages was

demonstrated with evidence of dyspnea in 31 cases. In 11 instances, there was evidence of pressure on the esophagus, but dysphagia was observed only in four cases. In three of these, the dysphagia was mild and not a major complaint. In the fourth patient, dysphagia was the outstanding symptom. It is believed that the mobility and elasticity of the esophagus accounts for the infrequent occurrence of symptoms in this group of cases, whereas the trachea and bronchi, being more rigid, are more commonly compressed by external pressure with resulting dyspnea.

### Hiatal Hernia

Herniation of a portion of stomach through the esophageal hiatus is not uncommon. While dysphagia is frequent and sometimes is the only symptom, Vinson<sup>14</sup> pointed out the necessity of distinguishing this from other esophageal lesions as well as from coronary heart disease and intraabdominal lesions, especially chronic cholecystitis.

The two important diagnostic aids are roentgen ray examination and esophagoscopy. In the roentgen ray study, unless the patient is examined in the recumbent or Trendelenburg position, the presence of hernia may be overlooked. In all questionable cases, esophagoscopy is indicated. If the hernia is associated with symptoms, *surgical repair* should be recommended if the condition of the patient is satisfactory and the symptoms are sufficiently severe to warrant such a procedure. Even if symptoms are mild, surgical treatment is indicated if the patient is a good operative risk because there is a likelihood of increase in the size of the hernia, progression of symptoms, and there is also a greater risk of mortality as the patient grows older. In no case, however, should surgical treatment be

contemplated until the esophagus has been investigated completely and found to be free from any obstructive lesion.

In the cases not suited for surgical treatment, *passage of a sound* over a previously swallowed thread will give relief if dysphagia is troublesome. Repeated passage of sounds may be necessary if there has been a marked cicatricial stenosis. Avoidance of heavy evening meals and sleeping in a semi-erect posture may also diminish nocturnal discomfort.

### Peptic Ulcer of Esophagus

Peptic esophageal ulcers have been found in patients of all ages, but they are more common in adults. In a series of ten cases reported by Allison, Johnstone, and Royce,<sup>15</sup> the patients were usually middle-aged or elderly. Dysphagia was the outstanding symptom. Pain, hematemesis, and vomiting or regurgitation are not uncommon. The diagnosis usually is made by roentgen ray examination and esophagoscopy.

Treatment is not satisfactory and the authors were not convinced that any treatment given had resulted in the complete cure of their patients. Dysphagia has been dramatically relieved by *esophagoscopy dilatation*, but this must be repeated at varying intervals. Ulceration was painted with a 20 per cent solution of *silver nitrate*, but there is question whether any real improvement resulted. After dilatation, a strict regimen of bed rest and a Sippy diet was enforced for six weeks. The patients were encouraged to sleep in a sitting position to minimize acid regurgitation into the esophagus and extra fats in the form of cream or olive oil were given. By these means marked *symptomatic treatment* was achieved, but there always remained some radiologic or esophagoscopy sign of persistent ulceration.



### Cicatricial Stenosis of Esophagus

In presenting a series of 13 cases of cicatricial stenosis of the esophagus resulting from the accidental swallowing of caustics, Grez<sup>16</sup> emphasized the importance of early *gastrostomy*; that is, on the fourth or fifth day after patients have swallowed caustics and cannot secure adequate food or fluids. This has the advantage of placing the esophagus at rest and also allows the patient to receive an adequate amount of food. While treatment of the stricture should not be undertaken before the third week, fluoroscopy and esophagoscopy should determine the time when this should be instituted. Esophagoscopy should be delayed until after the third week following the accident because of the liability of producing hemorrhage or other injury to an esophagus already weakened by the caustic solution.

The author used peroral and retrograde methods of dilatation and placed emphasis on the details of the treatment, particularly with regard to allowing the bougie to remain *in situ* for a time.

The customary method of treatment of lye burns of the esophagus in a majority of institutions was to wait until the strictures developed and then to carry out some plan of dilatation. Gellis and Holt<sup>17</sup> directed attention to the method advocated by Salzer and reported their results in a series of cases. Of 41 treated according to the Salzer method, only one developed a stricture and all of these patients have been followed at least a year, while of 14 who received no dilatation, six developed strictures. The method consists of *dilatation with bougies* in the form of soft rubber catheters tapered and closed at the lower end, filled with lead shot and corked above. Beginning with a small size, the

bougies are increased until number 28 or 30 is reached or until difficulty is experienced getting the bougie down. Dilatation usually is begun at once unless there is great swelling of the fauces and is carried out daily for two weeks, then three times weekly for two weeks, twice a week for two months, once a month for six months, and then two or three times a year for several years. The results secured certainly indicate that this method is worthy of further investigation since dilatation by other methods entails a prolonged plan of treatment and is not entirely devoid of danger.

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## GASTROSCOPY

### Gastroscopy for Diagnosis

In an analysis of 1000 consecutive gastroscopic examinations made on patients in the military service, Gillis attempted to determine the value of the indications for gastroscopy and the assessment of dyspeptics. He expressed the opinion that in gastric ulcers, the gastroscope may reveal ulcers not otherwise demonstrable and it affords proof of healing more cheaply and accurately than any other method. In chronic gastritis, it provides confirmation not otherwise obtainable and enables differentiation of types and degrees of severity essential for satisfactory disposal of persons in the military service and also for treatment. Multiple gastric erosions are not demonstrable by roentgen study, but by gastroscopy lesions of some significance can be diagnosed and differentiated into the chronic and acute and disposal can be made accordingly. While these are the more numerous lesions, others, including gastric carcinoma, benign gastric tumors, postoperative dyspepsia, unexplained gastric hemorrhage, and achlorhydria, can also be diagnosed.

### Local Anesthesia for Gastroscopy

*Pontocain* is quite generally used as a local anesthetic, either in the form of a gargle or by instillation into the tracheobronchial tree, and is considered a safe anesthetic. A warning of possible danger from this, however, is contained in the report by Hansen and Stealy,<sup>19</sup> who employed it as a gargle to secure relaxation of the pharyngeal muscles preceding a gastroscopic examination. The patient, an adult aged 54 years, had received a preliminary sedative (*pentobarbital sodium*) one hour before the scheduled examination and 0.25 grain of *morphine sulfate* 15 minutes before the examination. Immediately preceding the gastroscopy he was given 1 dram of a 2 per cent solution of *pontocain* in physiological salt solution to gargle. None of the solution was swallowed. During this procedure the patient suddenly collapsed, respirations ceased, and cyanosis developed. The pulse remained regular. Within two minutes there were generalized convulsive seizures which lasted from 15 to 30 seconds. Artificial respiration and supportive measures were instituted, but in spite of these the heart stopped beating 1 hour and 13 minutes after the patient first collapsed. A complete postmortem examination was made, but this revealed no organic reason for the sudden death. Because of the manner in which death occurred and the absence of any demonstrable cause, it was believed to be due to an anaphylactic reaction to the pontocain in the gargle.

### Hypertrophic Gastritis

There is much confusion in the minds of most physicians concerning hypertrophic gastritis. With the employment of flexible tube gastroscopy, the diagnosis now is a common one, yet gastroscopists

do not all agree on the criteria for the diagnosis. In a series of 1300 gastroscopies, Benedict<sup>20</sup> made a diagnosis of hypertrophic gastritis without other gastric or duodenal pathology in 117 cases, an incidence of 9.0 per cent. The expert roentgenologist, using the relief technic, may aid in the diagnosis of gastritis, but the only positive diagnosis is made by gastroscopy and only by gastroscopy can a differential diagnosis be made between the superficial, atrophic, and hypertrophic forms of gastritis.

Complications resulting from the flexible gastroscope are rare and although a number of perforations of the stomach and one of the duodenum have been reported, there has been but one death which was unquestionably attributed to its use. Paul and Lage<sup>21</sup> reported a fatal case following examination by the flexible gastroscope. The procedure was carried out without difficulty and no complications were anticipated, but four hours after gastroscopy the patient complained of pain in his throat with difficulty in swallowing. Six hours later he had a chill and his temperature rose to 102° F. Later there was cyanosis and dyspnea with crepitus over the right side of the neck and upper portion of the chest anteriorly. At autopsy the anterior and posterior mediastinum and entire pericardium was found the seat of a fulminating cellulitis. The esophagus appeared normal and no perforation could be discovered, but it was believed that there was a small tear in the esophagus which was closed by serum or exudate and was responsible for the fatality.

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## GYNECOLOGY AND OBSTETRICS

### GYNECOLOGY

FREDERICK H. FALLS, M.D.

#### The Development of the Periurethral Glands in the Human Female

Huffman<sup>1</sup> studied the development of the periurethral glands from serial sections of the female fetus of 50 mm., 80 mm., 128 mm., and 224 mm. crown rump length, and of six adult female urethras. Anlagen of the periurethral glands were observed for the first time in a 50 mm. fetus. These anlagen appear as four small, solid buds arising from the ventral and lateral surfaces of the urethra above the müllerian tubercle. In the 80 mm. fetus, urethral gland anlagen are evident as numerous buds, without branches developing from the same urethral site. Branched glands are present in the 128 mm. fetus, but in this stage, as in the younger embryos, only in the area of the urethra above the müllerian tubercle. In the 224 mm. fetus the glandular arrangement is similar to that in the adult. At this stage the lower urethra reveals one diverticularlike pocket, but no glandular structures are to be seen arising from the vestibule or vaginal mucosa. In the

adult urethras studied, the orifices of all periurethral or paraurethral glands arise from the urethral mucosa. In none of the fetal or adult urethras examined in this series were any glandular structures observed arising from the urogenital sinus below Müller's tubercle in the vaginal epithelium nor in the vestibule. Huffman feels that the occasional small glands in the lower portion of the urethra are carried downward on the lips of the somewhat trumpet-shaped opening of the urethra into the upper end of the urogenital sinus. As a result, the indistinct union of the urethra and urogenital sinus makes it appear that these periurethral glands are of sinus origin. It appears from the material studied that the larger paraurethral ducts and glands (Skene's) arise from anlagen above the müllerian tubercle. That they are similar to the other periurethral glands in origin and structure, and that they, like the periurethral glands, are homologues of that portion of the male prostate which develops above the union of the mesonephric ducts with the urogenital sinus.

### The Distribution of Nerves in the Adult Human Myometrium

Hirsch and Martin,<sup>2</sup> by using the Goldner modification of the Masson trichrome stain, were able to trace the nerves of the uterine wall and study their relationship to: (a) The arteries, and (b) the muscle fibers of the uterine wall.

They found that the large nerve trunks enter the myometrium with the arteries and follow them through the uterine wall to the inner fourth of the myometrium, where they penetrate the muscles and connect up with the radial arteries in part, and in part go to the stroma of the endometrium.

Myelinated or sensory nerve trunks and nonmyelinated or motor fibers were demonstrated. The ultimate connection of the nerves and blood vessels were not demonstrated by this technic. They describe, however, small ovoid structures which were closely identified with the muscles and adventitial coats of the arteries, one of which was clearly attached to a nerve trunk. These were 90 by 30 by 15 microns and were composed of compact oval nuclei in the center of a fibrillar stroma.

The abundance of nerves in the body of the uterus and their intimate connection with the arteries and especially with the spiral arteries of the endometrium seems to provide a nervous tissue medium for effecting control of the vascular phenomena associated with uterine physiology.

### Dysuria and Nocturia in the Presence of Normal Urine in the Female

McKim, Smith, and Rush<sup>3</sup> review 152 cases of women having bladder symptoms without pyuria. They stress the importance of a careful history and general physical examination. If caruncle is found, hospitalization and thorough ex-

amination of the urethra, bladder, and upper urinary tract are advised.

The vagina should also be carefully examined for evidences of pathology, and especially for *Trichomonas vaginalis* vaginitis. Hemorrhoids should also be looked for, since their removal may completely clear up urinary symptoms in some cases.

Cysts and polyps of the vesicle neck are frequently found to be the causative factor.

They advocate a conservative attitude in the treatment of all cases in which any acute inflammation of the bladder is present.

Cysts and polyps are best treated by **high frequency spark cauterization**.

Cooperation between urologist and gynecologist preoperatively and postoperatively is strongly endorsed.

Postoperatively they advise conservative treatment to see if the patient will not void spontaneously; failing this, **catheterization** and weak **silver nitrate instillations** in the bladder are advocated, and if this fails, an **indwelling catheter**.

Varicose veins of the bladder mucosa at the trigone may also cause urinary symptoms. These are best treated by fulguration.

In this series of 152 urological patients examination revealed the following gynecological conditions: 17 fibroids, 7 complete and 5 partial procidentias, 20 malpositions, 3 unilateral ovarian cysts, 2 hypertrophic cervicitis, 1 bilateral salpingitis, 2 calcifications of the uterus, and 15 cystoceles with associated lesion.

Drugs such as **menthol** and **barbiturates** have seemed to be etiological in a few cases. In seven women who smoked cigarettes excessively and complained of dysuria and frequency, relief was noted on switching to another type of cigarette.

### Ectopic Pregnancy

Farell and Scheffey<sup>4</sup> have analyzed a series of 75 consecutive cases of ectopic pregnancy and compared them with a previous review of 82 cases. The incidence among gynecological admissions was 1.3 per cent in the present series and 1.6 per cent in the combined review. The majority of the patients were in the third decade of life.

One-third of the patients had either not conceived previously or, having conceived, did not carry the pregnancy to term. Gross evidence of chronic inflammatory change in the uninvolved tube was found in 40 per cent of the patients, and 26 per cent had had previous abdominal operations. This high incidence of inflammatory disease and the rôle that postoperative adhesions may play in causing mechanical hindrance, are important etiologic factors in the production of an ectopic pregnancy.

In 93 per cent of patients some form of irregularity of the current menstrual cycle was noted. The majority of those experiencing tubal rupture reported external vaginal bleeding before the expected menses, while the majority with tubal abortions and intact ectopic pregnancies gave a history of a "missed" period. Abdominal pain was experienced by all patients and the onset was most frequently observed from two to four weeks after the last previous period. Concomitant signs of pregnancy were infrequent. Pelvic masses were palpable in 59 per cent of the patients.

These writers found that in 22 cases where *curettage* was performed decid-ual reactions of the endometrium were present in nine. They feel that *peritoneoscopy* is a rational procedure and has much to offer in the confusing type of case.

Correct diagnoses were made in 76 per cent of the combined series, pelvic

inflammatory disease being the condition most commonly confused with ectopic pregnancy. In both series the total mortality rate amounted to 3.2 per cent, while the operative mortality rate was 1.9 per cent. Two patients, being moribund on admission, died before operation. The deaths in both series emphasize the danger of delayed operation in tubal pregnancy. The operative findings in this series were tubal rupture, 19 patients; tubal abortion, 40 patients; intact tubal pregnancy, 15 patients; ovarian pregnancy, 1 patient. Sixty-six of the 75 patients were not rendered sterile. Of 27 followed, only five conceived; two had miscarriages; two had a second ectopic; one carried the pregnancy to term. Prompt *operation*, and the use of *blood transfusions* and *plasma* to combat hemorrhage and shock, are important and efficacious means for decreasing the mortality rate.

### Epithelioma

#### Bowen's Disease of the Vulva

Knight<sup>5</sup> adds six additional cases of Bowen's disease of the vulva to the 26 cases previously reported in the literature. He is of the opinion that it is a distinct disease entity. The important characteristic criteria for diagnosis are: (1) Hyperkeratosis and parakeratosis; (2) acanthosis with marked thickening of the rete Malpighia, which appear club-shaped; (3) loss of stratification of the individual cells, complete disorientation of the individual cells commencing just above the basal cell layer and extending to the surface; (4) the presence of nuclear clumping, "corpus roudes," nuclear "grains," and mitotic figures; (5) an intact basement membrane; (6) marked vascularity of the subpapillary zone with round cell infiltration.

Bowen's disease is a superficial non-invasive intraepithelial epithelioma char-

acterized clinically by chronicity, pruritus, and having malignant tendencies when involving mucosal surfaces. Knight is of the opinion that the choice of therapy is *local wide excision*.

**Superficial Noninvasive Intraepithelial Tumors of the Cervix**—With the problem of early diagnosis in mind, Knight<sup>6</sup> reviewed all the data on 406 cases of primary squamous cell epitheliomata that had been observed on the gynecologic service of the Sloane Hospital for Women between January, 1927, and April, 1943. Seventeen of these 406 cases were early superficial lesions. In 10 of these 17, the diagnosis was made from the examination of curettings from grossly normal appearing cervixes in individuals with fibromyomata or chronic inflammatory disease of the adnexa. In only two cases were minute gross lesions of the cervix noted clinically, and both were interpreted as papillary erosions. In two cases, the disease had its origin in cervical polyps.

Symptoms in the 17 women were variable. In many cases, there were absolutely no symptoms which might arouse suspicion of an epithelioma. Eleven of these cases had irregular intermenstrual bleeding. The remaining six patients' complaints included profuse menstrual bleeding, abdominal mass, and dysmenorrhea. Two cases had polyps and nine had fibroids.

In none of these cases reported was there found any deep invasion. It is impossible to predict how long a latent period of intraepithelial development and superficial surface spread will last, and when rapid growth and invasion will be manifest.

The author emphasizes the fact that when performing curettage, the tissues from the corpus and cervical canal should be collected separately. The quantity of material removed from the cervical canal

by curettage in chronically infected cases which present epidermidization is rather more abundant than one would expect. He is of the opinion that when removal of the uterus is indicated, a total hysterectomy should be performed, especially in the presence of a diseased cervix. Among 538 cervical epitheliomata on file, 38 or 7.1 per cent were stump carcinomata, and may have been present at the time of supravaginal hysterectomy.

Knight concludes: (1) Early superficial noninvasive epitheliomata of the cervix occur more frequently than supposed. (2) These lesions not infrequently have arisen in tissue which has undergone squamous metaplasia. (3) These lesions tend to develop slowly over a relatively long period of time, and seem less malignant than the more obvious epitheliomata. (4) These lesions should be treated as vigorously as the more obvious epitheliomata, whether by radiation or surgery, or a combination of the two.

### Endometriosis

Endometriosis involving the rectosigmoid was found in 47 of the 117 cases of endometriosis examined by Jenkinson and Brown,<sup>7</sup> and they estimate that between 2 and 4 per cent of all women have some degree of such involvement at some time during their menstrual life. These endometrial implants may produce constricting lesions. The degree of obstruction is roughly proportionate to the duration of the endometriosis while under the active stimulation of the ovarian hormones. Of the 47 cases in this series involving the rectosigmoid, 21 had symptoms indicating some degree of obstruction. These symptoms may be masked or overshadowed by other symptoms of endometriosis. The age incidence is from 18 to 67. Thirty of the women were 30 years old or less. The average duration of symptoms before operation was



2.8 years. Thirty-eight per cent of the women were sterile, 81 per cent complained of dysmenorrhea of the acquired type. Weight loss was seldom noted. They complained of severe progressive constipation with pain low in the abdomen. Other symptoms were flatulence, abdominal distention, ribbon stools, cramps, and diarrhea at the time of menstruation.

Sigmoidoscopic examination reveals a puckered reddened and congested mucosa which rarely ulcerates; hence, rarity of rectal bleeding. Biopsy is usually not feasible, but when taken helps to exclude carcinoma from consideration. Cachexia and weight loss are rare.

The characteristic roentgenologic finding of constricting endometriosis of the rectosigmoid is a filling defect as shown by a barium enema with normal appearing mucosa. The stenosis is well circumscribed and involves four to seven inches of bowel. Other portions of the colon showed no disease. The involved portion of the bowel was fixed. It can be differentiated from carcinoma by occurring in a younger age group, associated sterility, menstrual abnormalities, long duration of symptoms, absence of weight loss and anemia, and exacerbation of symptoms during menstruation.

Infectious lesions usually may be differentiated clinically by fever, leukocytosis, weight loss, anemia, stool examinations, and bacteriological and serological tests. Roentgenologically, they show a relatively long filling defect with ill-defined borders, distorted mucosal pattern, and indefinite line of demarkation.

Patients under 35 should be treated conservatively. Radical treatment is usually necessary in people with rectosigmoid involvement and includes **removal of both ovaries**. Complete restoration of the bowel lumen follows castration.

**Primary Endometriosis of the Cervix Uteri**-Lash and Rappaport<sup>8</sup> stress the rarity of endometriosis of the cervix uteri in a review of five cases previously reported, and add a sixth case.

They point out that most cases involving the cervix occur on the posterior cervical lip as an extension from a vaginal or rectovaginal primary growth. Most of the cases had scars in the cervix or history of trauma. The clinical manifestations that caused the patient to consult a physician were bleeding or a brownish discharge. The irregular bleeding, menstrual pain, and age of the patient indicate the possibility of carcinoma being the causative factor. This suspicion may be heightened by finding a nodular hemorrhagic area on the anterior lip and some destruction of superficial cervical epithelium. They point out that secondary involvement of the cervix can only be ruled out when the entire uterus is available for study.

They propose five criteria for the diagnosis of primary endometriosis of the cervix uteri:

1. Localization of the lesion on the anterior lip of the cervix or on either side of the external os.

2. Presence of endometrial islands in the most superficial areas of the vaginal portion of the cervix, either immediately beneath the squamous cell epithelium or directly exposed to the surface.

3. Presence of endometrial islands within scar tissue.

4. Absence of clinical evidence of endometriosis of the uterus or rectovaginal septum.

5. Cessation of clinical symptoms upon the excision of the lesion.

The evidence seems to show that these tumors result from the transplantation of endometrial cells into lesions, traumatic as a rule, of the lower generative tract. They cite the work of Schmid



who transplanted endometrial cells into the vaginal wound in 19 cases after hysterectomy. Most of these cases had subsequent regular cyclical menstrual discharge.

They discuss the reasons for the rarity of endometrial implants in the cervix and lower generative tract, and conclude that three factors are mainly responsible:

1. Absence of sterile conditions.
2. Resistance of the intact squamous cell epithelium to implantation.
3. The frequent presence of some degree of infection in cervical lacerations and erosions.

**Adenomyosis of the Uterus**—There is great confusion in the nomenclature of adenomatous lesions. They are frequently termed adenomyoma, or internal or external endometriosis. Their incidence has been variously stated by different authorities, Frankel stating that they are 8 per cent the frequency of fibroids. This can only be determined by careful routine examinations of removed uteri according to a special technic, followed by carefully studied microscopical sections. The majority occur at or slightly beyond the period of reproductivity; 96 per cent were over 35 years of age, while in endometriosis 54 per cent were under 35.

In uncomplicated adenomyosis the uterus is slightly or greatly enlarged due to a diffuse, usually symmetrical, thickening of the myometrium around the islands of endometrial cells. Occasionally, there are cysts, usually small, but at times several centimeters in diameter, and they may contain blood. Microscopically, irregular strands or islands of endometrial cells which are usually perpendicular to the endometrial surface appear in the inner half of the myometrium. Around these glands are cells of a stroma which, even when present without glands, should provide a diagnosis of endometri-

osis. The glands rarely show tendency to bleeding. Periuterine adhesions, fibroids, and carcinoma of the body of the uterus are all potentially complicating lesions.

Various theories as to the etiology have been propounded: (1) The direct invasion of the myometrium by the endometrial cells; (2) that these lesions are islands of cells representing misplaced remnants of müllerian duct epithelium; (3) that they are mesonephric rests from the wolffian body; (4) fetal budding of the epithelium of the endometrium; (5) misplaced islands of fetal mucosa may appear; (6) the condition may result from the misplacement of gland tissue; (7) it may be accounted for by invasion of myometrium by glandular elements during inflammation of the uterine wall; (8) the cells may originate from peritoneum by further differentiation of mesothelium; (9) migratory (Sampson) spread of cells through blood and lymph channels with deposit in the myometrium may account for the presence of these cells.

Seventy-three cases are reported, an incidence of 8 per cent. In 49 per cent of these they appeared in the inner half of the myometrium. Stromal cells participate in the cyclic changes of the uterine endometrium, but the epithelial cells did not change. The lumens of the adenomyotic glands communicated with the endometrial cavity. The average weight of these uteri was 123.25 Gm. The endometrial stroma is an embryonic type of connective tissue capable, as these authors<sup>9</sup> think, of undergoing metaplasia to form the glandular epithelial cells of the endometrium. Since there is no submucosa, the stroma cells of the endometrium merge gradually with the myometrium, sometimes the line of contact being sharp, and sometimes vague and uneven. Since the entire uterus is

derived from the mesoderm, epithelial connective tissue and muscle cells have a common origin. It would seem that adenomyosis then is a process whereby myometrial cells undergo a metaplasia first to form stromal cell islands, and later to differentiate glandular epithelial cells within these stroma islands. These lesions are only rarely and incidentally associated with malignancy.

**Radium Therapy in Benign Uterine Bleeding**—This analysis is based on a series of 350 patients in the private practices of the authors, Rongy and Seley.<sup>10</sup> They conclude from their experiences that: (1) Uterine bleeding can be cured by curettage and intrauterine insertion of radium in properly selected cases; (2) in 285 patients the bleeding was accompanied by fibroids; in 65, no fibroids were present; (3) the average dose required to induce artificial menopause is 1800 mg. hours. A small dose of radium is preferable to a concentrated dose; (4) complete involution of the tumor took place in 81.4 per cent; partial involution in 16.8 per cent; five patients not affected by the radium; (5) it is not advisable to use radium in patients who suffer from essential hypertension and who have no other contraindication to surgery; (6) radium is contraindicated in cases in which the uterus is enlarged to more than a 14 weeks' pregnancy. It should not be used when a submucous fibroid is suspected nor is its use advisable in subperitoneal or broad ligament fibroids; (7) it is dangerous to use radium in patients who give a history of having had a pelvic infection; (8) the menopausal syndrome is not accentuated by radium; (9) the leukorrheal discharge is increased for a period of six to seven weeks in a goodly number of cases; (10) sexual relationship is less likely to be disturbed following the use of radium. The libido is

definitely not affected; (11) curettage and intrauterine radiation can be safely utilized in at least 35 per cent of patients suffering from uterine bleeding. It should replace abdominal hysterectomy in 25 per cent of cases, and vaginal hysterectomy in 40 per cent; (12) curettage and radium therapy should be performed by gynecologists, not by radiologists.

The authors advocate repair of the vaginal vault at the time of the radium insertion. Sixty-five patients had plastic operations on the vagina and cervix, and in seven the interposition operation was performed. The morbidity was not increased nor was the hospital stay prolonged.

### Syndrome of Fibroma of the Ovary

Meigs, Armstrong, and Hamilton<sup>11</sup> present two additional cases of Meigs' syndrome and are particularly interested in the character of the exudate both as to mechanism of development and in qualitative content of the fluid in the abdomen and pleural cavity.

Fluid in the abdomen accompanying fibroma of the ovary is a frequent finding and has been reported in all series found in the literature. The removal of the tumor does stop the formation of the ascites; therefore, there is a direct cause and effect. In some cases that have been reported, a tremendous accumulation of fluid was found in the chest with only small amounts in the abdomen, which in the authors' opinion is the source of the fluid.

In two patients 2 cc. of sterile India ink were injected into the abdomen, and chest taps performed later. In each instance, the fluid in the chest showed the same concentration of India ink as in the abdomen. The blood showed no carbon crystals. The probability is that the pathways are *via* the lymphatics. The identity of both fluids is similar, both in

protein concentration and distribution, suggesting that there must be a fairly free communication between the two cavities. It remains for joint investigation by thoracic surgeons and others to demonstrate the presence of diaphragmatic perforations of small or large size, the presence of the rarely reported pleuro-peritoneal tubes, and to determine the direction and degree of permeability of the diaphragmatic lymphatics.

### Primary Dysmenorrhea

Dysmenorrhea occurs in approximately 35 per cent of menstruating women. Primary dysmenorrhea is characterized by painful menstruation in the absence of demonstrable pelvic disease, and is thus differentiated from secondary dysmenorrhea. It begins at the menarche in 65 per cent and a few years later in 35 per cent of cases. The distress starts with the flow, and consists of lower abdominal cramps with or without backache, headache, nausea, and vomiting. It persists one or two days of the flow, and disappears, or is much improved, after the first baby. After the age of 30 in the nullipara it usually lessens in intensity, occurs irregularly, and tends to disappear near the menopause.

In reviewing the literature Randall and Odell<sup>12</sup> came to the conclusion that the strong contractions which have been demonstrated in the luteal phase of the first two days of menstruation are involved in the production of pain. They point out that Kurzrok found no pain occurred when the women had an anovulatory menstrual cycle.

As an analgesic they use the following prescriptions:

	Gm.	or Cc.
(1) <i>Acetylsalicylic acid</i> ..0.324	5	gr.
<i>Codeine</i> .....0.03	$\frac{1}{2}$	gr.
<i>Ergotine</i> .....0.0648	1	gr.
<i>Atrophine sulfate</i> ....0.00045	$\frac{1}{150}$	gr.

Made into one capsule.

	Gm.	or Cc.
(2) <i>Camphor monobromate</i> .....0.003	$\frac{1}{2}$	gr.
<i>Atrophine sulfate</i> ....0.00045	$\frac{1}{150}$	gr.
<i>Papaverine hydrochloride</i> .....0.016	$\frac{1}{4}$	gr.
<i>Acetophenetidin</i> .....0.194	3	gr.
<i>Acetylsalicylic acid</i> ..0.194	3	gr.

Made into one capsule.

The writers discuss the work of Sturgis and Allright, who produced proliferative changes in the endometrium by injecting estrogens, stopped ovulation, and cured dysmenorrhea in 70 per cent of cases so treated. They also point out that the work of Moir and of Kurzrok with intrauterine balloons shows a strengthening of uterine contractions in the latter half of the menstrual cycle (luteal phase), and that these account for the menstrual pain of the first two days.

They believe that there is no evidence that anatomical or developmental defects have any influence on primary dysmenorrhea, hence treatment for the relief of this symptom by changing these anatomical abnormalities is illogical and accomplishes nothing.

They advocate telling the patient that she is normal organically and suggest that she be given sedatives at the time of menstruation, until she has a baby which will permanently dilate the cervix, or until she approaches the menopause when the dysmenorrhea spontaneously improves.

### Vaginal Bleeding

**Pathology of Postmenopausal Bleeding**—Schwartz<sup>13</sup> carefully studied pathologic specimens of 114 postmenopausal women past the age of 50 who presented themselves because of vaginal bleeding, spotting, or staining. Of these, 59.9 per cent had benign lesions of the cervix or endometrium, while 43.1 per cent were malignant. This study was primarily concerned with the benign lesions.

The author concluded that the varied histology of the endometrium after the menopause reflects the variation in the terminal functional activity of the ovary. If menstruation and ovulation end together and abruptly, the endometrium will be of the atrophic type. If the terminal menstrual cycles are anovulatory, the hyperplastic pattern may exist even in the absence of postmenopausal bleeding. After estrogenic production ceases, the preëxisting hyperplasia may show marked regressive changes in the epithelium and stroma. Endometrial hyperplasia represented 7.0 per cent of the total. The cause for postmenopausal bleeding cannot always be determined.

**Association of Vaginal Bleeding to Organic Pathology** — This study deals with 3956 cases of bleeding in women before the menopause. The authors classify the causes of bleeding into: (1) Complications of pregnancy, 861 or 21.8 per cent of the cases; (2) cancer, 611 or 15.4 per cent; (3) benign tumors — chiefly fibromyomas, benign ovarian tumors and polyps; (4) erosions of the cervix; (5) malpositions, and (6) blood dyscrasias.

Endometrial patterns in relation to the bleeding are variable. Abnormal bleeding may occur in patients with grossly normal pelvic organs with the endometrial pattern of a normal cyclical phase. The various endometrial patterns found are described. Three types of atrophic endometrium are distinguished by Millen and Shepard<sup>14</sup>: (1) Endometrial pattern associated with an hormonal decrease resulting from castration or aging; (2) mechanical type found over a fibroid which is a thinned or flattened endometrium, and (3) a type resulting from a local endarteritis such as occurs in fibrosis uteri.

The other endometrial patterns encountered are the hyperplasia (Swiss-

cheese type) which may be produced by prolonged estrogen activity; hypertrophy without hyperplasia when hormone imbalances produce a decidua-like hypertrophy of the cells without hyperplasia; adenomyosis may exist with the endometrial patterns in all the normal cycles as well as hyperplasia and atrophy, and, finally, acute and chronic endometritis.

The type of endometrial pattern to the pathology present was so variable that the authors are of the opinion that abnormal bleeding is not caused by any one organic pathologic condition or endometrial pattern, but that it is rather a symptom frequently associated with one of these lesions and a principal one in motivating the patient to apply for relief.

### Endocrine Therapy

Hamblen<sup>15</sup> reviews the present trend in the use of the endocrine products in obstetrics and gynecology, and attempts to evaluate their application to various obstetrical and gynecological problems. He prefers to group the hormones into two general categories: (1) Crystalline steroids which comprise hormones of the gonads and adrenal cortex or their derivatives, and certain nonhormonal synthetic chemicals with endocrinelike properties; (2) extracts of protein or protein-like nature derived from the pituitary and thyroid glands, and from certain body fluids.

The steroids include four groups: **Estrogens, androgens, progestational steroids, and adrenal cortical steroids.** The estrogens include three commonly used hormone steroids, **estrodial, estrone, and estriol**, and the nonhormonal steroid, **diethylstilbestrol**. The author discusses the various methods of administration and cautions against the use of implantation pellets in women with intact uteri.

A brief review of the indications and technic of substitutional and complementary estrogen therapy is discussed in the following conditions: (1) Hypo-ovarianism originating during adolescent years which may result in sterility and cosmetic inelegances; (2) in anovulatory ovarian failure during adolescence associated with prolonged and excessive uterine bleeding; (3) intercurrent ovarian failure during the reproductive epoch, manifested by sterility or prolonged and excessive bleeding; (4) palliative therapy during the climacteric; (5) opposed or antagonistic estrogen therapy or in certain instances of hyperpituitarism or hyperfunction of the adrenal cortex with virilism; (6) contraphysiologic therapy, as in menstrual headaches, dysmenorrhea, and periodic breast pain, and therapy during pregnancy and the puerperium. Other conditions where estrogens have been used, such as gonorrheal vaginitis, atrophic rhinitis, acne, and laryngeal papillomas, are mentioned.

Since instances in which the diagnosis of carcinoma was coincidental to prolonged estrogen therapy have been reported, Hamblen emphasizes the rationale of caution in estrogen therapy until the concept of carcinogenesis has been clarified.

Androgenic therapy with its grave virilization phenomenon has little place in the therapeutic armamentarium at present.

Pregestational principles include *progestin* and *progesterone* which the author finds of value in the conservative treatment of prolonged or excessive uterine bleeding of a functional nature and for the relief of afterpains. Hamblen is of the opinion that its use in preventing abortions and relieving dysmenorrhea is questionable.

The adrenal steroids are indicated in acute dehydration of the pernicious vom-

iting of pregnancy, and in pre- and post-operative care for patients requiring surgery. The efficacy of *desoxycortico-sterone acetate* in protecting against surgical shock has not been established.

The endocrine extracts of protein or proteinlike nature include the gonadotropins and desiccated thyroid glands. The *gonadotropins* include the *pituitary*, *chorionic* and *equine* types. In the administration of these proteins the possibility of sensitivity and anaphylaxis must always be considered. A discussion of indications, methods, and value in adolescent estrogenic failure, in anovulatory failure, and in corpus luteum failure are presented. The author emphasizes the importance of endometrial biopsy in the evaluation of the therapeutic results.

The uses of *thyroid substance* in amenorrhea, functional uterine bleeding, endocrine sterility, and in preventing abortion are well established and recommended.

**Octofollin** — Roberts, Loeffel, and MacBryde<sup>16</sup> treated 60 cases with some symptoms due to menopausal imbalance; 44 of these were treated sufficiently regularly to be included in this report; 30 of these were spontaneous and 11 artificial menopause following operation, and three had primary hypogonadism. Since small doses (0.5, 1, and 2 mg.) gave little therapeutic effect, 5 mg. was the usual dose used daily, and in a few cases twice or thrice daily. Of 26 cases receiving continuous treatment, five received the estrogen between one and three months, eight between three and six months, five between six and nine months, and eight for nine months or longer.

Eighteen received interrupted treatment for 14 days, followed by a rest for two weeks, then repeated treatment in doses of 1 mg. daily, and the next month 2 mg. daily. These small doses gave no

relief, and were increased to 5, to 10, and finally to 15 mg. in succeeding months. Treatment lasted for five months in seven cases and for seven months in 11 more cases.

The results could be considered good in 23 cases, fair in ten cases, and poor in four, with no improvement in one. It took 5 to 10 mg., however, to equal the results obtained by 1 mg. of *stilbestrol*, and much less toxic reaction as shown by nausea, vomiting, heartburn, and leg cramps was noted.

Significant changes occurred in the vaginal smears in 50 per cent of the patients treated by the continuous method. The 18 women receiving interrupted courses of treatment had some but less pronounced changes in the vaginal smears. It was impossible to correlate the changes in the vaginal smears with the degree of symptomatic relief experienced by these patients. Several patients noted some tenderness in the breasts, and an increase in areolar pigmentation.

When the larger doses were used in women receiving interrupted treatment, uterine bleeding occurred in three out of 18 cases.

Hepatic functional tests showed no significant change in liver function attributable to the administration of *octofollin*. Blood studies showed normal values for leukocytes, red cells, and hemoglobin.

Repeated urine analysis showed no changes that could be ascribed to the use of the drug.

Two dogs were injected with 5 mg. of octofollin for 50 days which caused a slight increase in the peripheral leukocytes but no thrombocytopenia. The dogs were then given 15 mg. for 14 days which caused a fall in the thrombocytes of the peripheral blood of one of the dogs; 20 mg. were then given for 16 days which caused a slight thrombocytopenia in the smaller of the two and a

slight reduction in the larger. Autopsy revealed no significant change in the bone marrow of either animal. Approximately one-quarter the amount of stilbestrol, estrogenically equivalent, has been shown to produce leukocytosis, thrombocytopenia, and death in dogs.

The authors conclude that this estrogen is effective clinically in the relief of hypogonadal symptoms, and that it is relatively nontoxic; 5 to 10 mg. daily is an effective dose for continuous treatment, and 10 to 15 mg. for interrupted treatment.

Hufford<sup>17</sup> used *octofollin* administered in dosage of 1 mg. by mouth and also by injection intramuscularly of an oily preparation varying from 2 mg. twice a week to 5 mg. a week. The compound is a 2-4-di (parahydroxy phenyl)-3 ethyl hexane. The advantage of this compound over *stilbestrol* seems to be that it is without toxic by-effects, as shown by liver function tests and the clinical response of the patients taking the drug. The amount and frequency of the dose varied with the severity of the symptoms and the response of the patient to the drug. Vaginal smears were taken and indicated an improvement in the vaginal cell cornification in almost all cases. Many patients showed improvement on octofollin treatment who had failed to respond satisfactorily to other estrogens.

In several cases hypertension, which was present before octofollin therapy, showed decided improvement after three months' treatment. Joint pains also were improved.

Undesirable side reactions, such as headache, nausea, vomiting, dizziness, soreness of the breasts, pelvic pain, and excessive or frequent uterine bleeding, were not encountered as a result of the treatment, although such complications had been repeatedly observed with stil-



bestrol therapy, both by oral and parenteral routes of administration.

**Effects of Estrogenic Therapy Upon Ovarian Function**—The present widespread, contraphysiologic usage of estrogens in women in whom no proven ovarian failure exists suggests the need for a clearer definition of the after-effects of this empiricism. The fact that recovery of full ovarian function results in a goodly number of women who had had prolonged or excessive estrogenic bleeding, and who had been treated with a cyclic estrogen-progesterone schedule, raised the question whether or not direct ovarian stimulation had occurred from what appeared to be essentially a complementary or substitutional régime.

Thirty healthy women between the ages of 16 to 35 years who bled from pregestational endometria were given estrogen therapy. Four estrogens, namely, *estradiol benzoate*, *estradiol dipropionate*, *estriol glucuronide*, and *diethylstilbestrol*, were employed; 61 cycles of therapy were administered during the first half of the menstrual cycle, fifth to fourteenth day; 15 cycles from the fifteenth to twenty-fourth day, inclusive.

Hamblen, Hirst, and Cuyler<sup>18</sup> found that the hormonal estrogens, with the exception of estradiol dipropionate, had no depressing effect upon corpus luteum function, presumably because of insufficient dosage. Estradiol dipropionate, which was given in larger doses, produced definite depression of corpus luteum function which was equal in degree to the depression produced with diethylstilbestrol, 66.7 per cent.

The authors conclude: (1) That certain hormonal estrogens, if given intramuscularly in adequate amounts, will depress corpus luteum function; (2) diethylstilbestrol, even in moderately small amounts used by mouth, will depress

corpus luteum function; (3) this depressing effect is not cumulative and does not persist after therapy; (4) the only direct effect of therapy on the ovarian level of function was the depression of corpus luteum function; (5) the other effects of therapy on the cyclicity and duration of bleeding probably resulted from direct action on the endometrium.

**Oral Hormonal Treatment of Functional Amenorrhea**—Cinberg has been able to produce bleeding in many cases of functional amenorrhea by the oral administration of *estrogen* and *progesterone* in combination.

A series of 18 patients, five cases of primary and 13 cases of secondary amenorrhea, were treated, in all but one of whom careful diagnostic survey failed to reveal the cause of the amenorrhea.

Estrogens were administered parenterally when the study was first begun and consisted of a series of five daily intramuscular injections of *estradiol benzoate*, 0.33 mg. each. This was followed immediately by five daily doses of 60 to 80 mg. of *pregneninone* by mouth. When the estrogens were employed orally, *stilbestrol* was given for five to ten days in doses varying from 1 to 3 mg. daily. Several consecutive courses at monthly intervals were given to each patient. A total of 62 courses of treatment were given to 18 women and resulted in 55 bleedings; five of the 18 women menstruated regularly after their courses of therapy were completed, but these were all young, average age of 22, and were extremely feminine individuals completely free of all endocrine stigmata.

Cinberg<sup>19</sup> found the endometria to be of interest; two specimens were obtained from each of 12 of the patients. All showed the absence of secretory endometrium before treatment. The post-medication specimens of three patients



exhibited secretory changes but these were all of the mixed variety and these three patients began to menstruate regularly after their treatments were completed. In six patients the endometrium revealed proliferation after therapy and in three there was atrophy.

The author feels the best method of therapy consists in the oral administration of 1 mg. of stilbestrol twice a day for five days, to be followed immediately by 60 mg. of pregnenolone daily for five days. The entire course of medication should be repeated at least three times to secure the best end results.

**The Value of Mixed Conjugated Estrogens in the Treatment of Menopause**—Neustaedter<sup>20</sup> has been using a water soluble orally active preparation of the estrogens derived from pregnant mare's urine in the treatment of the menopause. The predominating component in this preparation is *estrone sulfate*, although presumably smaller amounts of equelin and other estrogens in mare's urine are also present. The product is standardized by chemical, colorimetric, and biologic assay, so that each tablet contains 1.25 mg. of conjugated estrogens of pregnant mare's urine.

Sixty women were treated, eight of whom did not return for follow-up; 11 patients had artificial menapauses, and 42 had normal menapauses. The usual menopausal symptoms were present. Repeated vaginal smears were taken before the onset and during treatment.

All patients were given three tablets daily until all flushes were completely under control, and the minimal maintenance dose determined clinically. Treatment was discontinued during bleeding or menstruation.

The average time required for alleviation of symptoms was ten days, and all patients described a sense of well being. All but two patients tolerated the prep-

aration well, and symptoms returned when medication was discontinued.

Vaginal smears taken before therapy showed various pictures from that of mild to severe menopausal changes. These smears usually become highly cornified with the elimination of cellular debris within seven days. However, clinical improvement did not always parallel the smear changes. Neustaedter feels that if larger doses, which seem unnecessary for symptomatic relief, were used, all smears would show a high type of cornification.

**Testosterone Propionate and Methyl Testosterone in Dysmenorrhea and Menometrorrhagia**—Jacoby and Rabbiner<sup>21</sup> present the effects and results obtained by the administration of *testosterone propionate* and *methyl testosterone* in a series of 20 cases of dysmenorrhea, and a series of 15 cases of menorrhagia or menometrorrhagia. The treatment of the dysmenorrhea group consisted of 10 mg. of testosterone propionate administered intragluteally every other day, beginning two weeks before the expected onset of menstruation. The period of observation was from two to seven months. Four patients experienced complete relief during the period of observation; eight experienced partial relief, and six experienced no relief. Of the 12 patients who were relieved, seven had a recurrence of pain upon discontinuance of treatment.

In the menorrhagia and menometrorrhagia group, 25 mg. of testosterone propionate were administered intragluteally every other day, starting at least two weeks prior to the expected onset of the menstrual flow. Of nine patients followed, six experienced complete relief of excessive flow, two were partly relieved, and one showed no change. Practically, in all instances there was a recurrence of the original ailment after

discontinuation of treatment at variable intervals.

Oral androgenic therapy, if administered in adequate dosage, yields the same result as parenteral therapy.

**Androgen Therapy in Pelvic Malignancy**—Beecham<sup>22</sup> administered *testosterone propionate* to six patients with far advanced pelvic malignancy. The pain experienced by these patients (four of whom had ovarian carcinoma and two had cervical carcinoma) was almost completely relieved in the majority of cases, and constitutionally they were much improved, as evidenced by gain in weight. Similar results cannot be expected by opiates or irradiation. None of the cases demonstrated reduction in size of the neoplasm, nor were there histologic changes. The author feels this empiric therapy would be interesting to try in similar cases.

### Intractable Pruritus Vulvae

**A New Treatment**—A solution consisting of *procaine*, 2 per cent; *benzyl alcohol*, 5 per cent; in a vehicle of olive oil, peanut or almond oil, was used for injection in 15 cases of intractable pruritus vulvae.<sup>23</sup> The injection is made subcutaneously in four directions along the length of the labia majora and minora on both sides, across and above the area of the clitoris, and across the lower portions of the vulva above the anal region; 5 cc. of solution are used for each labia laterally, and 2.5 cc. for the upper and lower injections.

In from three to seven days the subjective symptoms are diminished or have abated and the patient is relieved. Occasionally a severe case may require a second injection. An interval of two to three weeks should have elapsed and only half of the original amount of solution should be injected. Although the vulva will present slight tumefactions of

a fibrous consistency, these disappear within two to four weeks. There was no sloughing or infections, but one patient developed an allergic cutaneous reaction which extended to the lower abdomen. The 15 patients who were injected were completely cured or markedly relieved.

### Vaginitis

**Treatment** — Allen and Baum<sup>24</sup> treated 282 patients for vaginitis, 83 of whom were pregnant, by the vaginal instillation of a *buffered acid, water dispersible jelly*. The infecting agent in 166 patients was the trichomonas alone; in 16, trichomonas and monilia, and in 40, neither gonorrhea, monilia, or trichomonas was found.

In 22.6 per cent of the trichomonas cases, trichomonas were found in catheterized urine specimens. Cystoscopic examinations were made wherever possible and repeated when indicated. Cystoscopic findings were usually characterized by inflammatory changes around the neck of the bladder. Acute infections were frequently associated with petechial hemorrhages about the trigone resembling acute trichomonas infection of the vagina.

The technic of therapy included the installation of 5 cc. of the jelly deep into the vagina at bedtime or twice daily. The standard for cure consisted of three consecutive negative smears obtained at the end of at least a three-month period. Thus, 115 were considered cured while 239 patients were symptom-free.

The authors are of the opinion that a buffered acid jelly is an effective method of the treatment of vaginitis and a shift of vaginal pH can probably be produced. The treatment of concomitant urinary tract infection is an important factor in the treatment of vaginitis. The addition of various chemicals have not appreciably increased the ultimate cures. The addi-

tion of *sulfanilamide* or *sulfathiazole* in amounts varying from 3 to 30 per cent was no more efficacious than the basic jelly, except that the smears seemed to show a more rapid disappearance of cocci. The authors find it difficult to explain the cure of so high a percentage of monilia cases (40 cures in 60 patients) by an acid jelly. The authors feel that the jelly offers a safe method of treating vaginitis during pregnancy.

**The Local Use of Acid Media and Sulfa Drugs**—Roblee's<sup>25</sup> purpose in this publication was to determine whether or not the addition locally of the sulfa drugs to anhydrous lactose as a pH factor would produce a further differential action. Since sulfa drugs are neutralized by the para-aminobenzoic acid in pus, a large concentration of sulfathiazole or sulfanilamide is needed locally to produce any bacteriostatic effect. Sulfathiazole showed no clinical evidence of absorption from the vagina or cervix. The author used *sodium sulfathiazole* alone with a pH of 9.6 to 12, and caused sloughing of the cervical mucosa in ten cases and cervical erosion in 12 patients. However, when combined with an acid medium or acid vehicle, it became sulfathiazole, losing its sodium ion.

Roblee obtained best results following conization of the cervix by packing the newly coned area with a sulfathiazole pack which is held in against the cervix by a vaginal pack of beta lactose. In 112 cases of conization of the cervix with the above technic, and additional post-operative treatment consisting of 5 to 10 cc. of the jelly inserted into the vagina every night the first two weeks and every other night the second two weeks, results were markedly better than were obtained with any previous method studied.

Seventy-one patients with vaginitis were observed; 28 patients received buffered acid jelly applied with vaginal ap-

plicator nightly for two weeks. There were 15 per cent failure; 15 cases (with 12 per cent failure) received 10 per cent sulfa jelly; 18 received 20 per cent sulfa jelly applied with vaginal applicator nightly for two weeks, then every other night for two weeks (8 per cent failures). In 61 cases the cervix received no treatment. In addition ten cases of monilia were treated with buffered acid jelly alone, with complete disappearance of the monilia; four other cases were treated with 10 per cent and 20 per cent sulfa jelly with one failure.

Roblee concludes that: (1) The bacteriostatic effect of sulfathiazole and sulfanilamide is demonstrated by local applications to cervix and vagina without appreciable absorption; (2) controlling the vaginal pH to 4 to 4.5 by the addition of buffered acid jellies is of value in the management of cervicitis and vaginitis, especially the trichomonas type of vaginitis; (3) combining the sulfa drugs and buffered acid vaginal jellies gives the most effective therapy in cervicitis (conization postoperative management) and vaginitis of all types; (4) conizations of the infected cervix may be safely performed in cases of acute gonorrhea when positive cervical cultures have persisted after oral administration of sulfathiazole, providing sulfa drugs in acid media are used locally during the healing period and at the time of conization. Negative cultures will then be the rule.

### Sulfonamides

**Acute Salpingitis**—Barrows and Labate<sup>26</sup> are primarily interested in the efficacy of *sulfathiazole* and *sulfanilamide* therapy in gonorrheal infections below and above the level of the internal os. All patients were given a course of 1.360 Gm. (21 gr.) of either sulfanilamide or sulfathiazole in a period of seven days. If smears failed to become

negative, a second course was given, and occasionally a third course. Thus, 204 cases of acute salpingitis were studied. Of these, 71 were admitted during a primary attack and 133 during an acute exacerbation of chronic salpingitis. Seventy per cent of the mild acute primary cases (adnexal masses under 5 cm. in size) and 66 per cent of the acute moderate primary cases (adnexal masses over 5 cm. in size) with an initial attack of less than five days' duration, showed complete resolution of the adnexal masses within one week of therapy. Primary salpingitis of over five days' duration, and recurrent salpingitis in the moderate or severe groups, showed no adequate response to chemotherapy. However, gonococcal urethritis and endocervicitis responded well to the sulfanilamides, and showed negative smears within the first week of treatment. The authors are of the opinion that permanent tubal damage may be prevented or minimized if chemotherapy is started within five days of an initial attack of adnexal disease.

**Local Use in Certain Gynecological Operations**—Richards<sup>27</sup> evaluates the results in 46 abdominal operations where sulfonamide drugs were used intraabdominally. He compares the results with a similar group of operative procedures where sulfonamides were not used.

In 13 cases of total abdominal hysterectomy, 3 Gm. (45 gr.) of powdered drug were placed beneath the layers of the broad ligament, and beneath the anterior bladder flap and 3 Gm. (45 gr.) in the *cul-de-sac* about the operative site. The second group included 14 cases, each of adnexal disease without contamination of the peritoneal cavity. Usually about 5 Gm. (75 gr.) of **sulfonamide** were placed about the operative site, and in the lower abdominal cavity. The third group included 14 cases each of adnexal disease with gross contamination of the

peritoneal cavity. A total of 10 Gm. (150 gr.) of sulfonamides were used in each case.

In none of these groups was there any evidence to support a conclusion that the drugs exerted any valuable effect.

The fourth group of cases included preoperative pelvic or generalized peritonitis. There were five cases *in toto*, all of whom were acutely ill at the time of operation. Of four adnexal cases, one patient died who refused operation until 16 hours after a large tubo-ovarian abscess was believed to have ruptured. However, in this group no suitable cases were found to use as controls. Richards feels that in this group of cases liberal use of sulfonamide drugs may be of value, since only one patient died in a condition which carries such a high mortality rate.

### Malignancy

**Clinical and Pathological Properties**—Goodall<sup>28</sup> studied several cases of extremely early malignancy of the female genital tract and found that there was no transition between normal to malignant tissue. Malignant cells have a property of heightened cell-division which is transmitted from cell to cell only through parent cell to daughter cells, and not by propinquity or contiguity.

The susceptibility of the patient determines the progress of any malignant process. The susceptibility is biochemical, be it endocrinological or metabolic, whether these be hereditary or acquired. Different tissues differ in time and degree of yielding their immunity to malignant cells.

In the majority of malignant cases, the cells are constantly invading the blood stream and are destroyed for various periods by the body. Local territorial cancer is usually met by resistance outside that territoriality. This territorial re-

sistance determines the rate of the metastasizing process. Simultaneous bilateral incidence of metastasis could be explained on frequent blood invasion, similarity in biochemistry and predilection of certain types of malignant cells in bilateral organs.

### Tuberculosis

**The Female Genital Tract** — Browne<sup>29</sup> discussed the etiology, frequency of site affected, symptomatology, and treatment of tuberculosis of the female genital tract.

Of the 15 cases of tuberculosis of the female genital tract reviewed by the author, the following observations were made:

**Age**—This averages out at 27 years.

**Marriage** — Seven were married women, two had been married for less than six months, while the remaining five had been married for at least two years before the diagnosis had been established. Of these, there were two parous women.

**Symptoms**—The most constant features were sterility, transient menorrhagia, and other menstrual disturbances; constant lower abdominal pain, and leukorrhea. Persistent amenorrhea or menorrhagia were not present.

**Preoperative Diagnosis**—Of the 15 cases studied, only four correct preoperative diagnoses were made.

**Operation** — *Bilateral salpingectomy* was usually performed, except where there was troublesome uterine involvement. The ovaries were conserved whenever possible.

**Primary Focus** — Contrary to the general opinion, only three cases exhibited tuberculosis elsewhere. Every attempt was made to detect it.

**Site of the Disease** — Tuberculous salpingitis was most frequently encountered; next was the involvement of the

ovaries, while involvement of the endometrium was third. There were no cases of tuberculous cervicitis, vaginitis, or Bartholinitis.

**Results**—All patients enjoyed good health without immediate or late complications, if sterility be excluded. This proves nothing but is strongly in favor of the surgical treatment of the condition. In no instance has remaining tuberculous endometritis nor proven tuberculous salpingitis been found to coexist with pregnancy in either site. In view of this and the serious nature of the disease, the author recommended *total hysterectomy* and *bilateral salpingo-oophorectomy* to avoid further complications.

**Unsuspected Tuberculosis of the Endometrium**—Three varieties of tuberculosis of the endometrium are recognized.<sup>30</sup> The first type, which is quite common, forms part of a widespread genital tuberculosis which chiefly affects other pelvic organs. In the second type, which is rare, the tuberculous infection is gross but is confined to the body of the uterus. The endometrium is replaced by a layer of tuberculous granulation tissue. The third type, which is generally thought to be still rarer, is also limited to the body of the uterus, but on microscopic examination, the tuberculous lesions are isolated and infrequent. The author, however, found that the third type is relatively common.

In 6385 specimens in which the endometrium was studied histologically, tuberculosis was found in 1.1 per cent. The tuberculous specimens were obtained from 58 cases, 24 of which were of the first type, one of the second, and 33 of the third. The second and third types (34 cases) form the subject of the present study. In all cases in this series there was nothing to suggest preoperatively that uterine tuberculosis was present.

The principal complaint in 24 patients was sterility; in nine instances there were profuse and sometimes irregular menses; the main complaint in the remaining patients was vaginal discharge. Thirty-two of the 34 patients were married and only five had had any previous pregnancy. Apparently tuberculosis confined to the endometrium is much more common in nulliparous patients. The chances of finding tuberculous lesions in the endometrium probably increase slightly towards the end of the menstrual cycle. Twenty sterile patients had tubal insufflation performed and tubal obstruction was found in 16 cases. In five out of 16 sterility cases in which the endometrium was removed premenstrually, a periodic or total anovulatory cycle was found.

In an average follow-up of three years, pregnancy has not occurred in any of the 28 patients traced. Gross spread to other pelvic organs was found once in 25 patients examined vaginally; two cases developed tuberculosis of the spine; 17 cases had x-ray examination of the chest, and four patients had evidence of the disease.

**Endometrial Tuberculosis as a Cause of Sterility**—Genital tuberculosis is more frequently seen in younger women between 16 and 25 years of age. The diagnosis is frequently made accidentally, especially if the patient has no other obvious tuberculous lesions. The presence of a hypoplastic uterus and an associated sterility is frequently noted. It is dangerous to do salpingography in these cases because of the danger of lighting up adnexal tuberculosis. In 208 cases of sterility, endometrial biopsy was done by curette, and in some cases that showed microscopic evidence of tuberculosis, a guinea pig was inoculated.<sup>31</sup> All positive cases were studied for other lesions of tuberculosis.

Twenty cases showed endometrial tuberculosis in the form of epithelioid tubercles and giant cells. The surrounding stroma showed the normal cyclic changes except for some round cell infiltration. Cultures and animal inoculations were positive in the few cases in which they were tried. The lungs were examined clinically and by means of x-ray in 18 of the 20 cases. All were negative for evidence of tuberculosis. The sedimentation rate was found normal in the ten cases examined. Gynecological examination revealed no evidence of genital tuberculosis. One woman was primarily amenorrheic, another had not flowed for six months, a third menstruated every three to four months. In 12 there was no menstrual irregularity. Sterility was the only reason these women sought medical advice. If thorough curettage had been done instead of strip curettage, more cases would probably have been discovered. It is a question whether the endometritis or tuberculous salpingitis is the cause of the sterility in these cases. The endometritis is probably always secondary, but whether by lymph, blood stream, or direct extension from the tubes is not certain.

The lesion should be treated conservatively, since caseous endometritis almost never ensues. Radical removal of the organ is not indicated.

**Intrapelvic Tuberculosis**—Tuberculosis constitutes 7 per cent of the inflammatory diseases of the pelvis. It is never primary, being always secondary to tuberculosis elsewhere in the body. The disease is essentially a descending infection. Spread by intercourse has never been proven. With the exception of miliary tuberculosis in which the bacilli are probably blood borne, pelvic tuberculosis arises from contamination of the peritoneal cavity by microbes from the primary focus.



Pelvic tubercular peritonitis may be divided into three groups, namely:

1. General tubercular peritonitis.
2. Slight cryptic local pelvic tuberculosis.
3. Nonreactive peritoneal cavity invasion.

When peritonitis occurs, either the pelvic organs are sufficiently resistant to overcome the infection or it spreads to the tubal mucosa.

The tubal infection usually takes on two distinct clinical types:

1. Mucosal disease.
  - a. Moist tuberculous pyosalpinx.
  - b. Nodular salpingitis.
2. Diffuse interstitial salpingitis.

Uterine infection is relatively rare, as compared to tubal involvement, and these cases usually heal spontaneously when the tubal disease has been removed or has healed spontaneously. Uterine infection is always secondary to tubal involvement. Its favorite sites are the cornua and at the shelf of the internal os.

The ovary is seldom involved as an isolated organ. The capsule of the ovary is impervious to the bacilli except by direct plastic contact, and invasion by contiguity of diseased organs.

Cervical tuberculosis is relatively rare. The diagnosis of tuberculosis of the pelvis is difficult and at times impossible, except by laparotomy. It may be readily confused with other subacute or chronic inflammatory diseases, peritoneal endometriosis, and malignancy.

There has always been a question whether tuberculosis of the pelvic organs should be treated differently from other types of inflammatory diseases. Goodall's<sup>32</sup> opinion is that it should be decidedly conservative.

Is it to be inferred, then, that operation is never indicated in pelvic tubercular disease? That is the desideratum, but that attitude cannot always be

adopted. It is safer to explore than to allow the diagnosis to remain in doubt. However, one should back out as soon as the diagnosis has been confirmed. There are very few exceptions to the rule, for example, tubercular pyosalpinx.

Goodall has been led to conservatism by the knowledge of five facts:

1. Patients do not die of pelvic tuberculosis if not operated upon.
2. When operated upon, they are susceptible to secondary infection.
3. Heroic surgical treatment in advanced cases is rarely happy and often fatal.
4. The most advanced cases of pelvic disease respond surprisingly to general rules of treatment as laid down for tuberculosis in general.
5. Noninterference has the advantage of not producing any deleterious effect upon the primary focus.

### Schistosomiasis (Bilharziasis) of the Female Genital Tract

There are three common varieties of human schistosomiasis. *Schistosomum haematobium* (Bilharz, 1851) and *Schistosomum mansoni* are found in Africa, while *Schistosomum japonicum* is found in the Far East.<sup>33</sup>

Man is infected by the pathogenic schistosome in two ways: (1) Exposure of the surface of the body to infected water; (2) exposure of the mucous membrane to infected water, *e. g.*, drinking. All schistosomes enter the mammalian host through the skin or mucous membrane to reach the blood vessels or lymphatics. Having penetrated the body of the host, they reach the right heart, pulmonary vessels, left heart, and then into the general circulation. The adult worms migrate to most of the large abdominal veins. In the case of *Schistosomum haematobium*, the gravid females find their way to the submucous tissue



of the genitourinary system, the bladder in particular, and deposit the eggs.

The essential pathological changes occurring in the tissue include: (1) Local hyperemia; (2) "sandy patches"; (3) local interstitial hemorrhage; (4) bulbous edema; (5) papilliferous changes; (6) ulcerations; (7) fibrosis.

The ovary is not a common site of primary bilharziasis, but is usually secondary to tubal or broad ligament involvement. Tubal involvement is rather common. Myometrial and endometrial bilharziasis are rare. The broad ligament is a common site, and is characterized by extreme thickening and fibrous changes. The cervix, vagina, and vulva present all the features of bilharziasis. Vesicovaginal fistula is relatively common.

The clinical features depend on the site of involvement and include the general symptoms of malaise, anorexia, and dyspepsia; menstrual loss; dysmenorrhea; suprapubic and low back pain; increased frequency of urination; sterility; pruritus, and vesicovaginal fistula.

In the pathological investigation, it is important to digest the tissue with caustic potash and look for the ova. It is more accurate than ordinary histological study of the specimen.

Most cases of genital bilharziasis require *surgical treatment* of some variety. For vesicovaginal fistula, *ureteral transplants* may be necessary.

In all cases, the urinary tract should be carefully studied.

The disease is treated with a preparation of *antimony*, preferably *via* the intravenous route. The initial dose is 0.03 Gm. ( $\frac{1}{2}$  gr.) and the dose is gradually increased to 0.13 to 0.16 Gm. (2 to  $2\frac{1}{2}$  gr.). Injections are given on alternate days until a total amount of 1.62 to 1.944 Gm. (25 to 30 gr.) have been given.

## Tumors

**The Krukenberg Tumor** — In 1896 Krukenberg described a peculiar type of ovarian tumor which occurred usually bilaterally, of considerable dimensions, and maintained the form of the ovary. He thought these were a form of sarcoma. Many of the cases had ascites. Microscopically, the growths showed typical cells of a signet-ring character due to eccentric position of the nucleus. Krukenberg failed to recognize the close resemblance to carcinoma, and the frequency with which it is associated with secondary carcinoma of the ovary, and in some cases the close relationship to carcinoma of the stomach.

There are primary Krukenberg tumors of the ovary, but these are not nearly as common as the secondary type.<sup>34</sup> Since Krukenberg's original report it has been shown that the primary tumor is most frequent in the stomach, and may be so small as to take serial sections to demonstrate. A total of about 78 cases have been reported. They occur at all ages from 14 to 66, the oldest on record, although they are most common in the ages of 20 to 30. Race plays no part in increasing the frequency, and single women are just as apt to have the tumor as married women, and multiparity does not appear to play a rôle.

Grossly the tumors are solid, maintain the shape of the ovary, are usually of moderate or large size, but may be so small as to be overlooked grossly. Sometimes cystic cavities appear. The surrounding capsule is smooth, and does not become adherent to surrounding structures. The cut surface may appear myxomatous and firm with gelatinous areas. Cyst formation with hemorrhage may occur. Microscopically, there are seen large polyhedral or rounded cells with mucoid contents compressing the

nucleus to one side, giving the signet ring appearance. These cells may be diffusely scattered among the ovarian stroma cells. The epithelial elements may appear as clusters of acini, and show varying degrees of mucoid degeneration. The original gland pattern may be entirely blotted out in some areas, and the original tumor cells in the primary tumor may show no evidence of mucoid degeneration.

The evidence seems to show that these metastases travel to the ovary by means of the lymphatics or the blood stream, since the earliest tumors found seem to originate in the medulla rather than the cortex of the ovary where one would expect to find them if they were implanted from the peritoneal fluid or by direct continuity of tissue.

A surgeon operating for gastrointestinal tract malignancy should palpate the ovaries in all cases before pronouncing the case free from metastasis.

**Parvilocular Tumors of the Ovary**—Schiller<sup>35</sup> calls attention to the cystic ovarian tumor first described by Pfannenstiel as a special type of adenoma which he called a solid adenoma. He defined this tumor as an ovarian tumor which grossly looks solid, but microscopically presents innumerable small adenomatous or tubular formations embedded in a fibromatous structure. He described the first case he studied as follows:

"In pseudomucinous cystomas of larger size sometimes solid parts can be found, which microscopically consist of very small cystic cavities lined by one row of typical pseudomucinous epithelium, and separated from each other by a small amount of connective tissue. The little cysts contain pure pseudomucin. Sometimes the 'solid' part predominates over the cystic, so that the tumor correctly may be called a 'solid' adenoma."

Pfannenstiel mentioned two cases of his own material and two others referred to him by other doctors. Kermauner had one case which was referred to him and neither this or others reported by Pfannenstiel showed any evidence of malignant change. Schiller's first case presented all the criteria described by Pfannenstiel and Kermauner, but in addition had larger cystic cavities. Some had papillary proliferating projections which eventually broke through the surface of the ovary to form metastatic nodules on the peritoneum, and resulted in the death of the woman. Schiller's second case was almost a duplicate of the first—definitely malignant. His third case was a fibrocystadenoma with typical parvilocular areas which occurred in a 69-year-old woman. The ovarian pedicle had become twisted and the woman died of shock. There was no evidence of malignancy.

Schiller then differentiates very carefully between these parvilocular adenomas and various other ovarian tumors, such as multilocular pseudomucinous cystoma, Krukenberg's tumor, mesonephroma, fibrocystoma, trabeculated granulosa cell tumor, and trabeculated arrhenoblastoma.

Schiller feels then that the parvilocular cystoma is an ovarian tumor characterized microscopically by small cystic cavities lined by a mucin-producing epithelium and embedded in a fibrous stroma. Papillomatous proliferation and carcinomatous transformation may be observed. The parvilocular adenofibroma presents ducts and narrow glands embedded in a well developed fibromalike stroma; it probably originates from fetal remnants of the rete ovarii.

**Mesonephroma or Teratoid Adenocystoma of the Ovary**—Stromme and Traut<sup>36</sup> report on ten cases of ovarian tumor in patients varying in age from 11 months to 68 years. They are not

convinced of the mesonephric origin of these tumors since they have not been able to demonstrate the structures resembling the architectural structure of the wolffian glomeruli, such as are shown in the retroperitoneal tumors which unquestionably are of wolffian origin. They are therefore inclined to view them as teratoid developments in the ovary which show some resemblance to mesonephric tissues.

Grossly, the oval tumors varied from 3 to 17 cm. in the smallest diameter. Cut surface shows degenerated portions forming cystic cavities. Papillary growths may penetrate the capsule or may remain inside the ovary, leaving the surface of the ovary smooth and not adherent to other organs. The cut surface is grayish yellow. Fat stains show fatty degeneration in places. Most of the tumors are relatively slow in growth. Dissemination may be by papillary outgrowth or by lymphatics to liver, bowel, spleen, or omentum. Free fluid may be present in the abdomen.

Microscopically, the solid portions of the tumors show closely packed acini and occasionally papillary tufts. The cystic larger spaces are lined by a single layer of cuboidal cells while the smaller spaces have hydropic cells of varying heights, depending on their secretory activity.

The solid portion of the tumors contains closely packed hydropic cells arranged in acini resembling somewhat collecting tubules. Here and there are papillary tufts extending into the acini. Occasionally are seen connective tissue structures lined by a single layer of flattened epithelium resembling the papillae of a serous cystadenoma.

In less differentiated tumors the cells form more papillae and fewer acini. The less the differentiation, the more mucin is secreted. The more malignant tumors

were more papillary in arrangement and showed less differentiation. Six of the ten cases here reported died or have extensive metastases. All were *operated* upon and six had *x-ray* treatment as well. Neither surgery nor x-ray seemed to help out in those cases with undifferentiated cells.

**Summary**—The tumors cannot be classed as of wolffian origin on the strength of the knowledge now at our disposal. They are much like the pseudomucinous and serous cystadenomas in the malignant forms, but not at all like them in the benign forms. The finding of serous, granulosa, and thecal elements makes it seem advisable to classify them for the present at least as teratoid cystadenomas.

**Mesonephroma of the Ovary**—Jensik and Falls<sup>37</sup> report a case of "mesonephroma of the ovary," bringing the total number of cases found in the literature to date to 28. They raise the problem of nomenclature and histogenesis and favor "Schiller's" designation of mesonephroma.

The term "mesonephroma" was suggested for the tumor because it was thought that the tumor arose from rests of embryonic mesonephron which were pinched off and retained in the subsequent developing gonad. Four reasons were advanced for this theory of the histogenesis of mesonephroma. First, that in the tumor the cells lining the cystic space are identical to the cells covering the papillary process, which arrangement is typical of the glomerulus of the kidney in which the epithelium of Bowman's capsule is reflected over the capillary loops. Second, in mesonephric glomeruli the paucity of capillary loops is striking. One, two, or three vessels constitute the tuft in contrast to the many loops seen in the glomeruli of the adult kidney. Third, reconstruction by serial

sections reveals the integral glomerular-like structure of the characteristic units found throughout the sections. And, fourth, the intimate relationship of the mesonephron to the developing gonad in the urogenital fold of 5 to 15 mm. embryos further lends plausibility to the theory of origin.

The appearance of the authors' case is unlike any other described endothelioma occurring extragenitally. There is a distinct separation between the blood vessels and the actual tumor cells as seen in the higher power photomicrographs. The endothelial lining of the blood vessels is quite distinct, and histologically different from the tumor cells surrounding the loop. Since a diagnosis of endothelioma cannot be made, the authors feel it would be better to establish a distinct entity from other forms of ovarian tumors with dissimilar structure.

Jensik and Falls, after reviewing the literature, feel that the evidence favors considering the tumor as an entity and that the term "mesonephroma" should be accepted at least until more evidence, pro or con, is forthcoming.

From the clinical standpoint Jensik and Falls emphasize the following factors: (1) This tumor can occur at any age. (2) The tumor does not have abnormal hormonal activity and does not cause feminizing or masculinizing symptoms. (3) The obvious malignant character of the neoplasm in the case presented further supports the impression of the tendency in this direction seen in previously reported cases. The lack of response to deep x-ray irradiation emphasizes the need for early clinical recognition and complete surgical removal. In all cases, a total removal of both uterus and adnexa and follow-up treatment with x-ray is indicated.

**Control of Carcinoma of the Cervix**—Since the inauguration of the Gynecology Tumor Conference in 1931 at

Ann Arbor, nearly 2000 cases of carcinoma of the female generative tract have been studied. Of these, 1235, or 65.8 per cent, were cervix carcinomas, all of whom have been followed. Miller<sup>38</sup> considers four factors arising from this study: (1) The quality of treatment; (2) clinical grouping; (3) causes of death, and (4) lay education and early treatment. He appreciates the fact that both irradiation therapy and surgery are powerful weapons, and if given opportunity may still accomplish what we have a right to expect in the way of greatly improved survival rates. Miller thinks results of therapy to date are disappointing.

The author feels that clinical groupings of the past have been inadequate. The League of Nations classification is too complicated, impractical, does not sufficiently emphasize the early lesion, and does not recognize the physical impossibility of definitely determining at a certain stage of the disease the presence or absence of parametrial spread. The weakness of Schmitz's classification lies in its too inclusive, ill defined first group. Miller suggests the following classification: *Group I.* Very early carcinoma of the cervix. In general this group includes the early suspicious, often unrecognizable clinically but histologically proved carcinomas of the cervix, *i. e.*, intra-epithelial lesions and carcinoma arising in a cervical polyp. *Group II.* Any clinically recognizable, histologically proved carcinoma still confined entirely to the cervix. No parametrial thickening. *Group III.* Carcinoma of the cervix with questionable parametrial thickening. The cervical lesion may or may not be extensive, the characteristic feature of this group being the question concerning parametrial involvement. Into this group are placed those patients concerning

whom there might well be a difference of opinion regarding the involvement of adjacent tissues. *Group IV*. All advanced carcinomas of the cervix. Those with definite parametrial thickening, vaginal infiltration, frozen pelvis, etc. This classification has proved its practicality and adaptability in the author's clinic.

As to the causes of death, 66 per cent of the cervix cases died of uremia due to encroachment of the neoplasm or scar tissue upon the ureters. Miller suggests *ureterointestinal anastomosis* judiciously performed as a means of prolonging life.

The author feels that lay education to the point of developing a symptom consciousness, next to a perfect cure, offers the greatest opportunity for early treatment and prevention of so-called precancerous lesions. Since it is estimated that the survival of cervix cancer decreases 16 to 20 per cent per month after the appearance of untoward symptoms, and in the author's clinic the pretreatment time waste averaged 6.4 months, the importance of education is apparent.

Miller recommends a color film which he produced for lay consumption, being of the opinion that if the average woman could be made aware of the cervix visually, the problem of maintaining its health would be nonexistent.

**Diagnosis of Cancer—*Endocervical and Endometrial Smears***—The diagnosis of cancer of the uterus by vaginal smears is based on the fact that, like all epithelial tissues of the body, the superficial cell layers of the tumor are subject to continued exfoliation. The exfoliated cells mix with the secretion of the uterus and cervix, find their way into the vagina, and may be recognized in a smear of vaginal fluid. Since the rate of exfoliation is variable with different types of tumors, a more valuable

study could be made from smears taken direct from the endocervical canal or uterine cavity. This fluid can be obtained by means of a simple cannula such as that described by Cary.

The authors feel the advantages of this method are: (1) The uterine smears show a larger number and greater variety of endometrial and cervical cells facilitating the diagnosis of cancer of the cervix and fundus; (2) it makes possible the procurement of uterine cells, even in the absence of bleeding. Papanicolaou and Marchetti<sup>39</sup> feel that the vaginal smear is such a simple method that they will continue its use routinely, whereas the endocervical smear will be applied more selectively in cases requiring additional study.

***The Vaginal Smear***—Meigs and his associates<sup>40</sup> have used the method of Papanicolaou for the diagnosis of uterine cancer by means of vaginal smear. They applied the method in 220 cases in order to obtain data which would either confirm or deny Papanicolaou's claims regarding the value of this procedure.

They point out quite correctly that delay in diagnosis is the most serious cause of mortality in carcinoma of the uterus. The average time between the onset of symptoms and operation is 7.5 months. They quote Bigelow and Lombard and also Todd to the effect that the chance of recovery decreases approximately 4 per cent a week after the onset of bleeding. Eleven of 100 women are diagnosed first in an operable stage, 29 are "borderline operable," and 60 are absolutely inoperable when treatment is begun. The delay is due to two causes: The patient does not report until four months after bleeding starts, and she is not operated on or treated until four months after she sees the physician. The latter waste of time is due to ignorance on the part of the physician, desire to

give reassurance, unfamiliarity with pelvic examination, reluctance to advise biopsy, ether examination, and curettage. They felt that if the method of Papanicolaou, which is a simple office procedure, were reliable that it could be used to hasten diagnosis and therefore save many lives.

*Technic*—A thoroughly dry suction pipette is inserted into the vaginal fornix of the patient, who has not douched for 24 hours. The material is blown out on a slide which is immediately dropped into a fixative (one-half ether, one-half 95 per cent alcohol) for five minutes or longer. They are run down through alcohols 70 per cent, 50 per cent to distilled water. Stained three minutes in Harris hematoxylin, dipped four times in solution of 0.5 per cent hydrochloric acid, and washed in running water and rinsed in distilled water. Passed through (50 per cent, 70 per cent, 80 per cent, 95 per cent) alcohol, then one minute in 0.5 per cent (orange G in 95 per cent alcohol), then washed twice in 95 per cent alcohol. Then two minutes in EA 36,\* washed three times in 95 per cent alcohol, absolute alcohol, xylol, and mount in Canada balsam.

The diagnostic criteria on which the decisions must be made in a given case presuppose a familiarity with the action of the stain on cells from the normal vagina. In general, it may be said that the cells from a patient with carcinoma are more irregular in size, shape, and form. The most striking cell is the greatly elongated "tadpole cell" which has a large head and a long thin body. These are long, thin, fiberlike cells with

elongated nucleus or two or three nuclei and tapered ends and are often found in groups.

The nuclei of carcinoma cells show marked variation in size and shape, and the chromatin material shows evidence of undue activity. Mitotic figures are rare but cells are frequently seen which are in the preliminary stages of mitosis. The nuclei vary markedly in size, often filling the cell, and often multinucleated giant cells are seen. Histiocytes with vacuolated cytoplasm are frequently seen. However, they are often seen in normal smears. Red and white blood cells may be ingested by the tumor cells. Red cells are always found in cancer cases.

In endometrial cancer there is not so great a variation in the size of the cells. Histiocytes and red cells are present, as are leukocytes. The nuclei of the tumor cells are larger, compared to the cytoplasm, and are hyperchromic. These cells frequently occur in clumps. Mitoses are rare. In some smears the tumor cells were so abnormal as to be easily recognizable; in other cases the variation from round cells was not great, so that the diagnosis could be made only after long study. In each positive case, when smears were taken from the surface of the tumor, the same types of cells were found as in the vaginal smears, which indicates that the cells found in the vagina were actual tumor cells.

Of 220 cases examined no tumor cells were seen in 153 who were examined because they were in the cancer age, or because of bleeding or discharge. These negative results were confirmed by operation or biopsy in 79 cases; in the remainder the clinical picture was not sufficiently suggestive to require operative procedures. Forty-six cases had cervical carcinoma, of which three were adenocarcinoma, three adenoacanthoma, the remainder epidermoid carcinoma. Of

\* EA 36 consists of:

Light green S.F.		
yellowish . . . . .	0.5% in 95% alcohol	45 cc.
Bismarck brown . . . . .	0.5% in 95% alcohol	10 cc.
Eosin yellowish . . . . .	0.5% in 95% alcohol	45 cc.
Acid phosphotungstic . . . . .		0.200 Gm.
Lithium carbonate, saturated aqueous solution . . . . .		1 drop

these 46 cases, 45 had positive diagnosis by vaginal smear test; 10 cases, or 22 per cent, were classified as early carcinoma.

There were 12 endometrial carcinomas, ten adenocarcinomas, and two adenocanthomas. Five could be called early carcinoma. Of the 12 cases, 11 were diagnosed by the vaginal smear; three cases of vaginal carcinoma and one of rectovaginal fistula and rectal carcinoma yielded positive smears. Of the 153 negative cases, four were reported positive for carcinoma in study of the vaginal smear—an error of 2.6 per cent.

More than one smear should be examined when a negative smear is obtained in a clinically suspicious case. Operation is not advised on the basis of positive vaginal smear alone, but such cases should be curetted or biopsy taken to prove or disprove the presence of carcinoma.

**Prognosis—Rise in Temperature in the Course of Radium Treatment**—Some patients suffering from carcinoma of the cervix show a rise in temperature during radium treatment. The consensus is that the rise in temperature is not due to the cancer *per se* but to the coexistent infection.

In a series of 909 patients, 37.5 per cent were found to have had a temperature of 100° F. or more during or after treatment. More febrile reactions occurred in more advanced cases. In the first stage cases there were 2 per cent of febrile reactions; in the second stage cases 23.8 per cent; in the third stage case 40 per cent, and in the fourth stage cases 58.7 per cent. Pyrexia, though a very frequent complication, is not an invariable symptom in more advanced stages of carcinoma.

Meigs and Jaffé stated that the tolerance of treatment and the general response of the patients have no prognostic

significance. This conclusion is not in accord with Goldscheider's<sup>41</sup> experience. The occurrence of pyrexia in the course of radium treatment is a bad prognostic sign. The immediate mortality rate is higher, while the five-year survival rate is lowered in patients who had a rise in temperature during or immediately after a full course of treatment.

**Treatment—Carcinoma of the Fundus of the Uterus**—Scheffey, Thudium, and Farrell<sup>42</sup> have treated a total of 127 patients with carcinoma of the fundus, and in this analysis include five-year end results in 75 of them. Of the total group 79.5 per cent were 50 years or older, and 20.5 per cent in patients under 50. Abnormal uterine bleeding was the most significant and reliable symptom in 90 per cent of the entire series.

The authors evaluate the end results under several groups: (1) Comparative results with each type of treatment; (2) composite results with all types of treatment expressed in absolute and relative figures; (3) comparative results in relation to grade of malignancy and type of treatment.

Sixteen patients were treated with **surgery** alone: Of 11 of these treated between 1921 and 1937, four survive the five-year period. There were two operative deaths among the first group of 11, but none in the later group of five patients. Sixty patients were treated with **radium** alone. Prior to 1937, 37 patients received 2400 to 3600 mg. hours of radium and external radiation of 1500 R to each of four portals. The five-year salvage in this group was 15, or 40.5 per cent. Since 1937, in 23 women the average dosage was 3600 to 5000 mg. hours, with external radiation; 16 of these have survived one to four years. Twenty-six patients were treated with **surgery and irradiation** before 1937 and 24 patients since 1937. The



five-year salvage in the pre-1937 period was 10 or 38.4 per cent and of the 24 later cases, 23 are alive from one to four years. The authors are of the opinion that preliminary irradiation with radium prior to complete surgery is rational treatment for carcinoma of the cervix.

The end results with all types of treatment in the group prior to 1937 reveals a five-year salvage of 38.6 per cent absolute and 39.1 per cent relative, while of the 52 patients treated since 1937, 43, or 82.6 per cent, are alive, while nine died within one year of treatment.

The authors feel that no absolute conclusions can be drawn with regard to the relationship of the grade of malignancy to the type of treatment. Low grade lesions respond equally well to irradiation and surgery, but it would seem that the survival rate in intermediate and high grade lesions is materially improved where irradiation has been a factor in the treatment, either singly or in combination with surgery. Prognosis based on the grade of malignancy alone is uncertain. It is only one of various factors that must be considered. With irradiation therapy it is the clinical response of the lesion that counts most of all.

**Panhysterectomy versus Irradiation**—The results of treatment in 704 cases of carcinoma of the cervix when *radiation therapy* was used are compared with those obtained after operation on a carefully selected group of 36 cases of early carcinoma of the cervix. The absolute cure rate, in these cases, of 41.6 per cent for the operated cases does not compare favorably with the rate of 57 per cent treated by radiation.<sup>43</sup>

The preinvasive type of carcinoma has also been treated by radiation with excellent results. Since many gynecologists and general surgeons still treat early carcinoma with *panhysterectomy*, these figures are a challenge as to the justifica-

tion of the operative procedure. It is emphasized that full radiation dosage must be given in order to obtain these results, especially since it has been found that many times the carcinoma extends much further than is appreciable by ordinary clinical examination.

EDITOR'S NOTE: The number of operative cases is far too small to be of clinical significance, and the operative experience of the surgeons doing the operations should be taken into account.

**The Effect of Preoperative Irradiation on Adenocarcinoma of the Uterus**—Schmitz, Sheehan, and Towne<sup>44</sup> present a technic for preoperative irradiation in adenocarcinoma of the uterus which they consider adequate. A comparison is made of results in patients adequately irradiated and those which, in their opinion, have been inadequately treated.

The technic described consists of *cu-rettage* followed immediately by the insertion into the uterine cavity of a Y capsule containing 50 mg. of *radium* element in each arm. After 2000 mg. hours, the capsule is removed. On the eighth and sixteenth days this radium dose is repeated, giving a total radium dose of 6000 mg. hours. On the days the radium is not inserted, the patient receives *x-ray* therapy. The dose attained within the pelvis after 28 days was 4000 R with backscatter.

Of 77 patients with adenocarcinoma of the uterus treated, 11 were *hysterectomized* after various time intervals following irradiation treatment, and the effect of the irradiation on the tumor and on the uterus was studied. Five of these cases were considered adequately treated and in none of these uteri was carcinoma found. The remaining six cases, inadequately treated in the opinion of the authors, all showed carcinoma.

Twenty patients were irradiated but not hysterectomized. The diagnosis was made on curettage and a third group of seven cases was diagnosed by other pathologists. The remaining 39 cases were excluded from the study, for they were first hysterectomized and then irradiated.

The 27 cases irradiated but not hysterectomized add further evidence, as demonstrated by curettage and follow-up, that adequate irradiation in clinical Group I or II carcinomas of the fundus had a definite value.

The authors do not advocate this treatment without hysterectomy in patients who are good surgical risks, but feel that their plan of preoperative irradiation should be carried on until sufficient case records are on hand to determine whether the five-year salvage is greater than in cases treated by surgery and postoperative irradiation.

**Multiple Primary Cancers of the Uterus**—Maliphant<sup>45</sup> discussed the criteria for multiple uterine carcinoma and presented a case of double uterine carcinoma.

The occurrence of multiple uterine carcinoma has been considered as an extremely rare phenomenon. Recent reports have supported the view that primary malignant tumors occurred more frequently than could be explained on the basis of mere chance. The incidence of multiple malignant tumors in paired organs and in functionally related organs is much greater than the normal expectancy.

From reports of multiple primary tumors occurring in the uterus it seems that the most common combination is that of carcinoma and sarcoma. Simultaneous growth of two carcinomas with distinct morphological characters in the same uterus is very rare.

Studies on multiple malignancy may shed some light on individual resistance

or susceptibility to carcinoma and to the rôle played by heredity on this disease.

**Sarcoma of the Uterus**—The incidence of sarcoma of the uterus has been variously stated from 2 per cent to 5.2 per cent. About one sarcoma is seen for each 48 carcinomas of the uterus, and one sarcoma for every 96 fibroids. There are two types of uterine sarcoma encountered in gynecological material, one a primary tumor arising from the connective tissue and muscle cells of the uterus, while the other much more frequent type comes from a sarcomatous change occurring in a degenerating myoma of the uterus. Figures up to 10 per cent of sarcomatous changes in myomatous uteri have been quoted, but the figure usually accepted is about 1 per cent.

Classification of sarcomas of the uterus is difficult because the early invasive type of growth makes it difficult to study the exact place of origin and spread. Therefore, it is necessary to classify them according to the dominant type of neoplastic cell. Thus we speak of giant cell, spindle cell, mixed cell, round cell, and endometrial sarcoma, and also sarcomatous degeneration of a fibroid. There is a varying degree of clinical malignancy in the various types of sarcoma seen. Giant, mixed, or round-cell type of tumor gave a grave prognosis, whereas spindle-celled sarcomas were relatively benign.

The diagnosis is rarely made preoperatively. Most of the cases have been found at operation, and were diagnosed fibroids before operation. They grow more rapidly than benign tumors, and have irregular bleeding and watery discharge. Pain has been noticed relatively early in sarcoma as compared with carcinoma. One of the most serious mistakes which leads to hopeless malignancy is to assume that abnormal bleeding from

a given uterus is due to a palpable but possibly incidental fibroid.

Effective treatment of sarcoma of the uterus depends upon *wide surgical removal*. The danger of postoperative thrombosis leading to embolism should be remembered, and care taken to avoid injuring the venous channels proximal to the point of ligation. After a subtotal hysterectomy for supposedly benign fibroids, when sarcoma is reported, there is always the possibility of malignancy in the remaining cervix. It is best to be conservative in the handling of such cases, since the removal of the cervix subjects the patient to greater danger than the probability of extension of sarcoma from the cervix. It is probable that in those cases in which sarcoma had already involved the cervix at the time of operation it would have extended beyond the removable limits, in which case secondary removal of the retained cervical stump would be useless. *Radium* to the cervical stump is much preferable in these cases.

After a review of the opinions of others on the effectiveness of irradiation treatment in sarcoma of the uterus, Randall<sup>46</sup> believes that it should be employed before *panhysterectomy* in the treatment of the highly cellular sarcomas of endometrial origin. On the other hand, he has found that *postoperative irradiation therapy* appeared to accomplish very little, especially in cases of the histologically more mature types of myogenic sarcoma.

Randall proposes a new classification, based primarily on the histopathology and clinical behavior, with the object of providing a practical basis for estimating prognosis in individual cases.

"Group A includes rapidly growing soft myomas containing a noticeable number of mitotic figures, but with preservation of a fairly regular arrangement

in spite of increased cellularity. In this group we would also place fibroids in which sections show atypical polymorphic or giant nuclear forms, usually in or adjacent to areas of degeneration in myomas. Fifteen patients in this group have been followed, nine for over three years and four for over five years with no evidence to suggest that a clinically malignant tumor was overlooked at the time of operation.

"Group B includes cases in which histologic section of a grossly appreciable fibroid reveals atypical nuclear forms and mitotic figures, evidences of the active proliferation of atypical cells. Twelve of these patients were noted as sarcomas associated with fibroids. Two additional cases, discovered in reviewing the histology of 1400 fibroids, had not been properly filed in the record room and are included here as the thirteenth and fourteenth secondary sarcomas followed. Obviously, Group B includes secondary sarcomas in myomas as well as primary sarcomas (belonging in Group C). We believe the majority of the clinically malignant tumors in this group are primary sarcomas associated with an incidental fibroid. For a practical estimate of the prognosis, if there was a grossly appreciable fibroid, we have placed the tumor in Group B.

"Group C consists of tumors frankly sarcomatous arising in uteri not containing fibroids. It is evident that a majority of patients with a true primary sarcoma of the uterus consistently run a rapidly fatal course.

"Group D comprises the small group of highly anaplastic tumors usually designated as carcinosarcoma. The literature regarding this particular group of tumors provides a comprehensive discussion of the various histologic pictures frequently classified as carcinosarcomas. Hoffman has called attention to the rarity in which

this picture is due to coexisting carcinoma and sarcoma in the same uterus. Handley and Howkins emphasize the difficulties of accurate diagnosis in this group of cases. They advise consideration of the possible effects of: (a) Secondary infection; (b) previous irradiation therapy, or (c) sarcomatous infiltration of a secondarily invaded and distorted epithelial surface. At least two of the three cases in our series were in all probability highly malignant anaplastic carcinomas. They are included here because we wish to mention later the comparative radiosensitivity of these tumors compared to other types of uterine sarcoma.

"We believe this proposed grouping provides a practical basis by which sarcomas of the uterus may be classified. Our observations suggest this grouping may prove an aid in estimating prognosis in the individual cases. The relationship between prognosis and the proposed grouping is indicated in the following outline:

"A. The presence of noticeable number of mitotic figures in rapidly growing myomas or the finding of giant cells—atypical polymorphic nuclear forms—in or adjacent to degenerating areas in leiomyomas, may be regarded as criteria warranting a suspicion of sarcomatous change, but neither finding alone should imply a clinically guarded prognosis.

"Patients in this group should not be considered as harboring a malignant tumor and so-called prophylactic irradiation therapy is not justified.

"B. Histologic evidence of actively proliferating atypical cells in patients with a grossly appreciable myoma—the presence of mitotic figures and atypical nuclear forms—warrants a diagnosis of sarcoma, arising either as a result of so-called sarcomatous degeneration in a fibroid or as a primary sarcoma associated with an incidental myoma.

"Patients in this group should be treated by radical surgery. A guarded prognosis should be given as recurrence or extension of a clinically malignant tumor may be expected in a definite proportion of these cases.

"C. Histologic diagnosis of sarcoma in a uterus not containing fibroids usually foretells a rapidly fatal course, irrespective of the type of predominating cell or the apparent histogenesis of the tumor. In a striking percentage of cases, operative removal of this type of tumor is followed by death from vascular accidents during hospital convalescence. Preoperative irradiation may decrease the number of post-operative deaths due to thrombo-embolism, but the majority of primary sarcomas of the uterus are relatively resistant to irradiation therapy, and usually only palliation can be expected.

"D. Certain highly anaplastic tumors of the uterus are frequently classified as carcinosarcoma. In a majority of these cases the histologic picture indicates a highly malignant tumor difficult to classify, rather than the presence of coexisting carcinoma and sarcoma.

"Patients in this group provide the more radiosensitive of the tumors classified as sarcomas of the uterus, but early extension or local recurrence is the rule. Death due to metastasis may occur in spite of apparent local eradication of the tumor.

**"Conclusions** — Fibroids showing areas of atypical cellularity should not be viewed with alarm unless the histologic changes justify a diagnosis of established sarcoma.

"The prognosis of patients with sarcoma of the uterus primarily depends upon the state of the disease when adequate treatment is instituted. To a lesser degree prognosis varies with the histology of the tumor.

"A comparatively simple basis for the classification of sarcomas of the uterus is suggested as an aid in estimating the degree of clinical malignancy.

"A general attitude of pessimism is not justified in the management of patients with sarcoma of the uterus. Among the patients followed in this study and in a majority of similar reports in the literature, the percentage of five-year survivals is approximately 30 per cent."

**Chorionepithelioma** — The pathology, clinical features, and treatment of chorionepithelioma were discussed by Murray and Ahmed.<sup>47</sup> Fourteen cases

were reviewed and the following observations were recorded:

1. The most complete uniformity of history and symptoms. It is stated that chorionepithelioma may not appear for several months or even years after the termination of pregnancy. The authors considered that the trophoblast will not invade the uterine tissue to a certain distance and then become dormant, only to wake up some time later. They felt that in patients in whom this seems to have been the case that another, unrecognized pregnancy of short duration has occurred. Careful questioning will elicit the fact that an excessively heavy period took place, or there was a sudden hemorrhage *per vaginam* a short while before the onset of the symptoms.

2. The rapid growth of the neoplasm. This was noted by observing the size of the tumor in relation to the duration of symptoms. The authors were not able to find evidence of the slow growth.

3. The high degree of malignancy. This was noted by the invasion of the tissue as seen microscopically, having due regards to the duration of symptoms.

4. The excellent response to treatment when uncomplicated by metastasis. The treatment is essentially **surgery** with deep **x-ray therapy** of the abdomen and pelvis later as a routine.

5. The deleterious effects that metastasis caused. After hysterectomy, secondary growths sometimes disappear spontaneously. But once the resistance to its spread is broken down it runs a rapid fatal course.

6. The extreme usefulness of the Aschheim-Zondek test. This test is valuable as a diagnostic aid, and also during treatment is a guide to the cure.

**Carcinoma of Bartholin's Gland**—Boughton<sup>48</sup> points out the rarity of reported cases that can be accepted as true cases of carcinoma of Bartholin's gland.

Although Bartholin's gland is part of the vulva it is distinctly encapsulated, and in the early stages of its development should lead to early removal and complete recovery. The history of these cases often shows that they have been neglected as far as early discovery and complete removal is concerned, because their true nature was unsuspected.

Honan, in 1897, suggested the following criteria to be fulfilled in making a diagnosis:

1. A tumor mass in the region normally occupied by the gland.

2. Gland deep in labia. No involvement of overlying skin.

3. Microscopic picture of gland tissue bearing some resemblance to Bartholin's gland structure or the presence of normal gland tissue inside the gland capsule, or connection with the gland duct.

Clinically, a tumor in the posterior third of the labia majora is suggestive. It usually is hard, nodular, and may be movable, but more frequently is fixed. Necrosis occurs, with softening of the tumor, which leads to the mistaken diagnosis of abscess until failure to heal after incision leads to a correct diagnosis. There are no symptoms in the early stages. All suspect cases should be under close observation, and the gland should be excised in all such women over 40 years of age.

Normally the epithelium of the gland is columnar in the alveoli and squamous at the opening of the duct; the rest of the duct is lined by a transitional type of epithelium. Under conditions of chronic inflammation a metaplasia occurs in the ducts and alveoli which results in squamous cells replacing the columnar cells. Metastasis to the inguinofemoral lymph glands, rarely to the deep nodes, usually occurs. Treatment should consist of **early and complete removal of the gland** and its immediately poten-

tially involved lymph glands. This offers the best hope for complete eradication of the carcinoma. A fatal case is reported and several photomicrographs of the tissue involved are shown.

### Posterior Vaginal Enterocoele

Posterior vaginal enterocoele is due to two main factors: An abnormally deep *cul-de-sac* of Douglas, a congenital defect, which permits of undue pressure against the *cul-de-sac*, causing traction on the posterior cervical lip and anterior rectal wall, resulting in downward displacement of the uterus and bladder or prolapse; the other responsible factor is the trauma of labor disrupting the thin rectovaginal fascia and forming a hernial sac which gradually becomes larger and larger.<sup>49</sup> A third less common cause is a hernia developing after a vaginal hysterectomy which has been done for prolapse of the uterus if the *cul-de-sac* is not obliterated at the time of the primary operation. This can best be done by approximating the uterosacral ligaments in their entire length after removal of the uterus.

It may also occur following an operation for prolapse of the uterus in which a cervical amputation is followed by anterior colporrhaphy, perineorrhaphy, and a ventrofixation of the body of the uterus. This leaves a wide space between the posterior surface of the cervix and the rectum.

There are two accepted methods of closing these hernias: The Marion-Moschowitz abdominal operations, by which the *cul-de-sac* is obliterated; the vaginal operation by George G. Ward, which consists of freeing the vagina from the rectum and from the cervix. The enterocoele is dissected up and the sac opened. The contents are emptied upward and the sac is transfixed, ligated, and resected. The uterosacral ligaments

are next approximated in their entire length, using fine silk or catgut for interrupted sutures. If the abdominal operation is done, a series of purse-string sutures obliterates the deep *cul-de-sac* from below upward, using due care not to incorporate the ureters in these sutures.

Forty-eight cases are reported upon. The follow-up was not complete on all cases. All had satisfactory results as examined when they left the hospital. Six per cent of the cases resulted in failure over a period of 20 years. The vaginal approach is advocated for most cases. The abdominal operation is done on large hernias.

### Vulval and Vaginal Surgery

**Local Anesthesia**—For gynecological surgery local anesthesia is seldom employed. Its full value has not been fully appreciated, nor is it realized that its application is extremely simple.<sup>50</sup>

The technic for various gynecological surgery of the vulva and vagina will vary from case to case. For a typical case (Fothergill colporrhaphy), the following technic was employed:

For premedication *morphine*, 0.016 Gm. ( $\frac{1}{4}$  gr.), with *scopolamine*, 0.00065 Gm. ( $\frac{1}{100}$  gr.), is given two hours before surgery, and scopolamine, 0.0003 Gm. ( $\frac{1}{200}$  gr.), 90 minutes later.

A point on the perineum  $\frac{1}{2}$  to 1 inch anterolateral to the anus is chosen and an intradermal wheal is raised; the needle is then pushed forwards, and the subcutaneous tissue of the anterior margin of the perineum is injected. A larger needle is then used and is slowly thrust into the perineum through the vesicle to a depth of 2 inches, in a direction at right angles to the skin surface, the anesthetic being injected as the needle advances and retires. The needle is almost withdrawn, and then directed forward, but quite superficially, underneath the

line of reflexion of the folds of the labia minora and as far as the anterior extremity of the proposed perineal incision. The procedure is repeated on the other side of the perineum, and about 10 cc. of anesthetic are injected into each. The object of the injection is to relax the superficial and deep muscles of the pelvic floor, and to anesthetize the deep perineal branch of the pudendal nerve.

A vaginal speculum is then inserted, and the cervix grasped with forceps. The larger of the needles is again used and the injection is made through the vaginal fornix close to the cervix and immediately lateral to it. Ten cubic centimeters of anesthetic are also injected here. The point of the needle must travel to the level of the internal os.

This completes the routine for most cases. Additional anesthetic may be required if further work is contemplated. For surgery about the *cul-de-sac* 2 or 3 cc. of anesthetic are injected between the epithelium and peritoneum. If removal of the uterus is required, an additional injection at the upper part of the broad ligament is required. The infundibulopelvic ligament will require injection if the ovary is to be removed. For repair of a urethrocele, 2 to 3 cc. of anesthetic are injected about the subpubic fascia.

Contraindications for local anesthesia include: (1) Acute inflammation; (2) anatomical obstruction to the site of injection; (3) pathological obstruction to the site of injections. The advantages include: (1) Very little hemorrhage; (2) no bad effects of the anesthetic; (3) applicable to patients with respiratory or cardiovascular disease.

**Construction of an Artificial Vagina**—Adams<sup>51</sup> reviews the various types of operation for making an artificial vagina and reports two cases in which a specially devised plug is used

to hold in place skin grafts that are applied to the walls of a cavity produced by dissection between the bladder and rectum. The skin graft was 3.5 inches wide and 7 inches long, was wrapped (raw surface out) around a rubber sponge tissue supported by a wire framework making a cylindrical plug approximately the diameter and length of a normal vagina. The graft covered plug was then inserted into the cavity prepared, and held in position for ten days. A retention catheter was placed in the bladder for an equal period of time. The mold was held in place by two tension sutures through the labia majora to prevent movement of the mold and displacement of the grafts. At the end of this time the mold was removed and the grafts were found to be well healed. An acrolite mold with perforated walls for drainage and irrigation was then used for a week to prevent contraction and thereafter a sponge mold covered by a condom was used. These molds remained in the vagina without special retaining binder. A comparative study of the vaginal epithelium of the artificial vaginal wall with that of a normal vaginal wall showed changes after a year which made it comparable to normal vaginal mucosa in all respects.

### Urinary Incontinence in Women

Counseller<sup>52</sup> emphasizes the importance of a careful analysis of the cause of the incontinence and a complete understanding of the anatomy of the vesical neck, urethra, and pelvic fascia, plus the normal physiology of micturition before undertaking any surgical corrective procedure.

The female urethra has an internal and an external involuntary sphincter and in addition a voluntary sphincter surrounding the middle third and extending posteriorly to cover the internal



urethral sphincter partially. This sphincter is designated the sphincter urethrae membranaceae (Gray) and is the same as the external urethral sphincter in the male. Kennedy's investigation of this sphincteric mechanism has served to clarify the real cause of incontinence, and he suggested a method of repair which has greatly improved the results.

The essential technic of the Kennedy operation consists in separating the urethra from the pubic rami on each side, keeping close to the bone to avoid a plexus of nerves and branches of the inferior vesical artery. This separation must extend into the paravesical space, thus establishing freedom of motion to the urethra. This freedom of motion is maintained by plicating the tissues under the urethra which will hold the urethra from the pubic rami. A second layer of mattress sutures through the fascialike structures on the lateral aspects of the urethra further separates the urethra from the pubic rami. A Kelly stitch plicates the inner portion of the urethra about the internal sphincter. Next, the voluntary sphincter is restored by passing the suture through the vaginal wall close to the pubic rami so as to catch the muscle fibers of the constrictor urethrae and inferior layer of fascia of the urogenital diaphragm.

Counseller has performed this operation on 26 patients, all of whom were completely relieved of their incontinence. The high percentage of failures when other methods of surgical repair were used should represent that group of patients who exhibit more damage to the sphincter mechanism than relaxation of the internal sphincter and proximal centimeter of the urethra.

### Vesicovaginal Fistula

Murray and Ahmed<sup>53</sup> discuss the importance of curing vesicovaginal fistula

from the patient's standpoint, and distinguish between the tears that occur and heal rapidly, spontaneously, and those which occur after difficult labors or operative procedures with secondary infection that results in tissue necrosis.

They discuss the edge paring technic of Marion Sims and the flap dissection method of more modern surgeons. They postulate several conditions necessary to operability:

1. The fistula must be in such a position that it can be thoroughly exposed to the view of the surgeon.
2. There must not be any serious constitutional and/or specific disease or same must be eliminated.
3. The fistula must be of moderate size.
4. The fistula must not be adherent to other pelvic structures, especially the bony pelvis.

If these conditions are not present it is better not to attempt to close the fistula, but to transplant the ureters into the pelvic colon.

A certain amount of differences of opinion regarding the operation itself has been recorded and, while some men agree with the authors that a two-stage operation is preferable, others are in favor of the one-stage operation. The objection to the one-stage operation is the onset of anuria with fatal results. The type of patients that are treated come from the poor and malnourished class, and are poor risks to serious and prolonged operations.

To minimize the danger of ascending infection, cases are carefully selected. Good pre- and postoperative treatment are important.

The result of the operation is excellent, the patients being able to retain urine in the rectum for two to four hours, the average amount being some eight ounces.

**Operation**—The right ureter is chosen for transplantation first. The abdomen is opened by right paramedian incision. The uterus is lifted forward. Small and large intestines are pushed above and aside from the field of operation. The right ureter is identified.

The ureter crosses the brim of the pelvis just near the sacroiliac junction, and makes peristaltic movements under the posterior peritoneum like a roundworm (vermiculate). The peritoneum at the optimal site is picked up and incised with a sharp scissors. Sometimes the ureter is missed when it is adherent to the posterior peritoneum. The ureter is picked up and separated from surrounding tissues, preserving very carefully the minute blood vessels which run along its surface, for its vitality will suffer if it is stripped of its blood supply. The pelvic part of the ureter is carefully traced behind the broad ligament up to the bladder, where it is clamped between two artery forceps, the vesical end being cauterized with carbolic acid and buried. The upper portion wrapped in a piece of gauze is for the time being placed out of the way on the anterior abdominal wall.

The upper part of the rectum which is selected for the implantation must be devoid of *appendices epiploicae*. An oblique incision is made on the antero-lateral wall of the rectum. The incision should be deepened as it proceeds downwards and all bleeding points are picked up with fine artery forceps and tied off. With a tenotomy knife a stab wound is made through the lumen of the rectum. The ureter is now brought forward from its resting place on the abdomen, and its end is shaped into a wedge, the portion that is cut away being taken from its posterior aspect. This wedge point is then transfixed and a long thread of catgut drawn through. There is a needle

at each end of the thread, which is to avoid tearing out of the catgut as a result of the tension caused by subsequent threading. These two needles are then successively introduced into the lumen of the bowel, and brought out through its anterior wall at least half an inch from the lower end of the stab wound. Traction now brings the shaped end of the ureter into the bowel and the threads are tied. The ureter now lies on the ventral aspect of the rectum in the gutter made for it, where it is anchored by two sutures passing through the cut edges of the original incision and the anterior wall of the ureter. Its upper freed portion is then buried after the method of Weitzel, peritonized by Lambert sutures, and finally fixed to the mesentery. The cut margins of the posterior peritoneum are repaired. Thus the ureter now lies in the wall of the rectum before it enters the lumen of the bowel, which arrangement is similar to its course in the bladder wall (an effective valvular control over the exit of urine). The abdomen is closed in layers. The left ureter is similarly dealt with four weeks later.

For the first ten days, steady and continuous drainage through the rectal tube must be maintained. *Magnesium sulfate* or other purgative salts are used to ensure that the feces are semifluid.

Sixty-five cases were reported. In 61 of these cases the operation was two stages, and in five, one stage; 51 cases, 78.5 per cent, were cured; 14 cases, 21.5 per cent, died. Out of 14 deaths, three occurred after the one-stage operation.

### Hysterectomy

**Total Abdominal Hysterectomy**—Foss and Babcock<sup>54</sup> review the literature, comparing the total abdominal hysterectomy with the subtotal operation.

They endorse the view that total hysterectomy shows definite advantages over the subtotal operation in competent hands. The mortality and morbidity rates for the two operations are about equal. The main advantage of the total operation is that the cervix, the site of infection or possibly a future neoplasm, is removed. They admit that the complete operation requires more skill, and that in the hands of inexperienced surgeons the subtotal operation is probably safer, even when the liability of malignancy developing in the retained cervix is taken into consideration.

They quoted Richardson's statistics of 2.3 per cent cervical stump carcinoma occurring in 940 patients with cervical carcinoma at Johns Hopkins University.

Meigs reported 2.13 per cent cervical stump carcinomas occurring in 1218 cases of carcinoma of the cervix.

They stress the danger in every total hysterectomy of: (1) Danger of injury to the ureter, and (2) injury to the bladder. Either or both of these may become apparent late in the patient's convalescence.

They discuss in detail the technic of their total hysterectomy and have excellent drawings showing the details of each step. They also show a number of special instruments which they have found useful in carrying out the technic of the operation.

**Technic**—The patient should have a cleansing douche administered the evening before the operation, followed by the introduction of a vaginal antiseptic that is germicidal but not irritating. The following morning, after the anesthetic has been administered, and the authors' preference is for spinal almost routinely, the patient is placed in the lithotomy position, and the vagina again is thoroughly cleansed. The solution used is one which they apply in abdominal skin

preparations. It was developed at the University of Minnesota by Novak. It is nonirritating, is powerfully germicidal, and has proved a most satisfactory medium. The formula for the cleansing solution is given as follows:

#### CLEANSING SOLUTION FORMULA

Alcohol (95%) .....	525.0	cc.
Acetone .....	100.0	cc.
Water .....	375.0	cc.
Tricresol (Lysol) .....	5.0	cc.
Mercuric chloride .....	9.7	Gm.
Eosin Y .....	0.6	Gm.
Acid fuchsin .....	0.08	Gm.

The patient is placed in the Trendelenburg position, and the usual vertical incision between the umbilicus and the pubis is made, which, in case of a large tumor, is carried to the left and above the umbilicus. After the peritoneum has been opened, and the wound is protected with towels, a Balfour retractor is inserted, and the intestines are gently packed off in the upper abdomen. Traction is then placed either upon the fundus or on the tumor itself. When the tumor is a myoma, a corkscrew type of retractor will be found particularly helpful. The ovaries are preserved, or removed, according to the indication, the patient's age, and the type of tumor. If the ovaries are to be excised, the broad ligaments are clamped, and the ovarian vessels are secured and ligated. The peritoneal reflexion covering the bladder and the anterior surface of the uterus is carefully divided, and the bladder is pushed well downward and anteriorly. This step is extremely important. The bladder should be thoroughly separated from the anterior surface of the cervix and the upper vagina, otherwise, in the later stages of the operation, there is a possibility of its being injured by the needle or by the right angle clamp to be described later. By carefully dissecting the bladder from the anterior surface of the cer-

vix, and holding it well forward by means of a retractor, damage to it can be completely avoided.

The incision is now carried down until the uterine vessels are exposed, at which stage they are clamped, divided in the usual manner, and secured by a transfixion suture. Meanwhile, the round ligaments have been divided close to the uterus and ligated. The stumps of the uterine arteries are then gently pushed downward by means of gauze sponges after which branches of the cervical arteries are secured and tied. The positions of the ureters are definitely determined and constantly borne in mind. While firm, upward traction is maintained on the uterus, the cellular tissue overlying the cervix is divided, the dissection being kept close to the cervix at all times, so as to avoid the ureters. Continuing the operation, the dome of the vagina is separated, anteriorly, from the cellular structures between it and the bladder as well as laterally and posteriorly, in the same manner. Areolar tissue attached to the cervix should be gently pushed down by means of a piece of gauze held in a pair of long finger dressing forceps. One must be sure that the ureters are well out of the way before application of the transverse vaginal clamp which is then applied across the upper portion of the vagina, immediately beneath the cervix, and locked firmly in position. By means of the angle knife the vagina is cut across immediately below the cervix and above the jaws of the clamp. The clamp completely prevents contamination from the vagina, and effectively controls bleeding from the cut margins of the vaginal walls. The tumor is then removed in one mass, together with the uterus and the cervix. The vaginal dome is next closed by means of a running mattress suture of chromic catgut placed back and forth beneath the

clamp in an anteroposterior direction; then the clamp is removed, the suture being continued back across the vaginal cuff so as to pick up the severed margins of the mucous membrane in an over-and-over running suture. At this stage, it has been their custom, before implanting the round ligaments, to sprinkle 0.5 Gm. (8 gr.) of *crystalline sulfanilamide* over the stump of the vagina and surrounding raw surfaces.

The ligaments are then approximated. Frequently, if sufficiently long, they are overlapped and firmly sutured into the dome of the vagina by means of interrupted sutures of catgut so as to produce an effective support. The whole area is then thoroughly peritonealized by means of a continuous suture passing from one round ligament to the other, and laterally from the dome of the vagina to the ligated ovarian arteries. Usually the lateral sutures are placed interruptedly for, if a continuous suture is used, there is danger of kinking and, possibly, of blocking the ureter.

They stress that if even a competent surgeon becomes careless in the performance of a total hysterectomy, complications develop which will completely offset the advantages of this operation over the subtotal operation.

**Vaginal Hysterectomy**—The tendency in many clinics to avoid vaginal hysterectomy because of unfamiliarity with the operation results in deficient training of internes and residents, and deprives many women of the advantages offered by this operation for the correction of the condition which they present. Since there is a growing tendency to advocate the total removal of the uterus when hysterectomy is advised, the advantages of the vaginal operation should be thoroughly appreciated by all operators. The operation avoids persistent leukorrheal discharge or bleeding from

the cervical stump, and eliminates the danger of the development of stump carcinoma.<sup>55</sup>

In 517 cases, the major indications for the operation were: Leiomyomas of varying size, usually small ones, 170 cases; prolapse of the uterus, 144 cases; uterine descensus of moderate degree, 112 cases; uterine hemorrhage, 53 cases; symptom-producing retroversion, 50 cases.

Vaginal hysterectomy is favored over radium or x-ray in nonmalignant bleeding from the uterus because it often gets rid of an infected or lacerated cervix, and avoids the sclerosing effect of these agents on the ovaries.

While large fibroids may be removed by morcellation through the vaginal route, this is not advisable if there are concomitant pelvic inflammatory lesions or if the operator is not thoroughly familiar with the technic of the operation. In prolapse cases the operation is indicated because it removes the pathological cervix, permits support of the bladder by interposing the upper as well as the lower portion of the broad ligaments, and permits of combating the occurrence of enterocele by uniting the uterosacral ligaments in their full length. The operation is especially valuable in old women because of the relatively slight amount of shock experienced. The cases with symptom-producing retroversion and those with moderate descensus and outlet relaxation are often best dealt with by vaginal hysterectomy which also eliminates discomfort from varicose veins of the broad ligament.

Contraindications to vaginal hysterectomy are: (1) Pelvic inflammatory disease; (2) previous pelvic operations with adhesions; (3) endometriosis; (4) ventrofixation; (5) associated ovarian cysts; (6) carcinoma of the body of the uterus, because of danger of spreading the can-

cer cells through the broad ligaments before they can be clamped.

The repair of the perineum, vaginal plastic, repair of urinary incontinence, all may easily be cared for after the uterus has been removed. The suture method is favored over the clamp method. No deaths occurred in these 517 cases. A morbidity of 42 per cent was noted. Drainage was not used except in those cases where third degree procidentia was the indication for operation. Serious complications such as bleeding, abscess, vesical or rectal injury, were exceedingly rare, and the vagina was not found to be appreciably shortened after the operation. Proper instruments are very helpful in facilitating the procedures during operation.

### **Prolapse of the Uterus and Vagina**

**Surgical Management**—The condition of uterovaginal prolapse is one of the commonest lesions encountered by the gynecologist. Because it produces much misery but rarely death, it is necessary to choose for its correction a surgical procedure with low mortality.<sup>56</sup>

Five fundamental factors determine the method of treatment: (1) The age of the patient; (2) the possibility of future pregnancies; (3) the extent of the prolapse; (4) the size of the uterus; (5) whether or not coexisting disease exists.

Seven hundred and thirty personally operated cases are considered. In 117 cases vaginal plastics and abdominal suspension or fixation of the uterus were done. While conceding the desirability of conservative treatment in women in the child-bearing age, if careful watch is kept of the cervical lesions which may lead to cancer, Phaneuf feels that the severe cases of prolapse will often have to be operated upon to obtain relief. The cervix is repaired as well as the anterior

and posterior vaginal wall and perineum.

The abdomen is opened, the uterosacral ligaments shortened, and the uterus suspended by the round ligaments. High amputation of the cervix and ventrofixation of the uterus should be avoided before menopause, because they predispose to sterility, abortion, dystocia, and miscarriage. After the menopause the fixation operation may give better support. The vaginal operation, however, is frequently selected because of less shock and complications. A combination of both methods is sometimes elected and in all of these cases a thorough repair of the pelvic floor for additional support is indicated.

In 224 cases, the *Watkins-Wertheim interposition operation* was done. It is contraindicated if the uterus is small and atrophic. It is necessary to cut the pillars of the bladder in this operation to prevent vesicle tenesmus, which will otherwise result. The retention of the uterus is an asset in repairing recurrence of the prolapse should it occur.

*Vaginal hysterectomy* with interposition of the broad ligament was used when the uterus is small and there is pathology present which indicates its removal. The broad ligaments are ligated in three sections on each side, the lowermost suture including the uterosacrals. These sutures are then tied with the corresponding suture of the opposite side. The *cul-de-sac* of Douglas is closed by approximating the uterosacral ligaments in their entire length with interrupted sutures. The broad ligaments are then sutured to the anterior vaginal wall after resection of the vaginal flaps of each side.

The *clamp method of vaginal hysterectomy* (Price-Kennedy) gives excellent results, is very rapidly done, and is especially advisable in older and feeble women. It is best carried out in two steps: (1) Removal of uterus and re-

pair of anterior vaginal wall, followed by (2) repair of pelvic floor two and one-half to three weeks later. Local anesthesia may well be used. The operation requires longer hospitalization which may even be an advantage in rundown patients.

*High vaginal fixation of the uterus* is especially valuable in recurrences following previous vaginal plastics and abdominal fixations. The anterior vaginal wall is opened and the bladder freed from the vagina and uterus. The uterus is pulled down and the bladder advanced high on the uterine wall with a suture, the ends of which are passed through the upper end of the vaginal incision and tied, thus raising the bladder high in the pelvis. After a high amputation of the cervix the remainder of the anterior uterine wall is sewed to the anterior vaginal wall followed by a perineorrhaphy. No failures in 57 cases so treated occurred.

The *Manchester or Fothergill operation* employs the principle of bringing the cardinal ligaments together in front of the cervix, which is amputated if necessary, plicating the musculofascial tissues attached to the bladder and resection of a wide flap of anterior vaginal wall, followed by a complete repair of the perineum. In 85 cases it has given excellent results, and has replaced the use of the interposition operation to a large extent.

The *LeFort or subtotal colpectomy* is especially useful in older women with atrophic uteri since it can be done under local anesthesia. Its one disadvantage is that the closure of the vagina precludes sexual relations, which is unimportant in this group of women.

*Total colpectomy* is reserved for the most extensive cases of inversion of the vagina in old women. Both this and the subtotal operation are fortified against

recurrence by the addition of a high perineorrhaphy.

In 54 cases a posterior vaginal enterocele was repaired. The large hernias were treated according to the *Marion-Moschowitz technic*, which consists of closing the *cul-de-sac* of Douglas by a series of purse string sutures of non-absorbable material, so placed as to avoid injury to the ureters. Moderate degrees of this hernia are better treated by the *Ward technic*, which is done vaginally. The *cul-de-sac* of Douglas is mobilized and the sac opened, the contents reduced, and the sac ligated and excised. The uterosacral ligaments are then approximated in their entire length, followed by a perineorrhaphy. The results are excellent.

The results in these cases were difficult to evaluate accurately because the distance the patients had come for operation rendered follow-up examinations difficult. It was also noted that late recurrences ten or more years after operation make it difficult to speak of cure in these women. In young women prolapse is best treated by cervical repair, vaginal wall plastic, perineorrhaphy, and round ligament suspension with shortening of uterosacral ligaments.

Postmenopausal women are handled by vaginal operation, only occasionally opening the abdomen to repair a recurrence or to obliterate a very large posterior vaginal hernia.

The interposition operation gives excellent results in properly elected cases.

Vaginal hysterectomy with interposition of united broad ligaments is used in women with atrophic uteri and where cancer is suspected.

Vaginal hysterectomy with the clamp method is used when operative time is an important factor.

High vaginal fixation is useful in first and second degree prolapse with large

cystocele, and when recurrence has followed an abdominal fixation.

The Manchester operation has supplanted the interposition and vaginal hysterectomy in many cases in recent years.

In feeble old women the LeFort subtotal or a total colectomy under local anesthesia is the operation of choice.

Adequate repair of the perineum is vital in all these operations, and posterior vaginal enterocele should be properly repaired.

**End Results of the Richardson Composite Operation**—There is as yet no uniformity in the treatment of uterine prolapse with its associated conditions such as diseases of the cervix, cystocele, urethrocele, rectocele, etc., where the future function of childbearing is not a consideration. Although individualization in each is desirable, various clinics have a tendency to utilize favorite operations routinely for prolapse and associated conditions. In one, vaginal hysterectomy is done routinely; in another, the Watkins Interposition, and in a third, the Manchester. TeLinde and Richardson<sup>57</sup> have been conservatively inclined towards vaginal hysterectomy, using it chiefly in cases where benign diseases of the corpus make it desirable to remove the organ.

They have used the interposition operation with excellent results but feel that it has certain disadvantages which the composite operation avoids.

1. The possible development of myomata, functional bleeding, or corporal carcinoma.

2. If removal is necessary, there are great technical difficulties involved when the uterus has become adherent to the anterior vaginal wall.

3. If the fundus is fixed well up under the pubic arch, the anterior vaginal wall is not as pliable as it should be.



The vaginal hysterectomy, in their opinion, also has limitations because of the frequency of recurrence of cystocele, prolapse of the vaginal vault and recurrent enterocele.

For these reasons Richardson, Sr., devised the composite operation here described, which the authors have performed with favorable results in 50 women. Of these, 33 were followed for from six months to five years; 23 of these were private patients, all of whom were completely relieved. Three of ten clinic cases were not completely relieved although the anatomic results were perfect.

The operative plan has as its objective:

1. Riddance of the hypertrophied and diseased vaginal portion of the cervix;

2. Extirpation of the corpus uteri, together with the tubes and ovaries if indicated;

3. Optional destruction or excision of remaining cervical epithelium;

4. Minimal trauma and devitalization of structures later to be utilized for reconstruction purposes;

5. Preservation of an assured and adequate blood supply to the several units;

6. Total ablation of associated enterocele through high obliteration of the *cul-de-sac* of Douglas;

7. Rational utilization of all supporting structures that experience has demonstrated to be helpful and dependable, namely, the pubocervical fascia, the basal portions of the broad ligaments, the uterosacral and round ligaments, the fascia of the rectovaginal septum, as well as the muscles and fascial layers of the pelvic floor and perineum;

8. Reestablishment of a vagina of normal depth and caliber, and

9. Restoration of normal relationships.

The essential features of the technic include the following: (1) The usual in-

verted vaginal T incision is made to the vesicouterine pouch of peritoneum and the pubovesical fascia is dissected. (2) Amputation of the cervix is accomplished and the posterior cervical lip covered with a flap of mucosa. (3) The vesicouterine pouch of peritoneum is entered, the fundus delivered, and a supracervical hysterectomy is performed. (4) The cervical stump is closed and the ovarian and round ligaments, together with the end of the tubes, are sutured to the angles of the stump. (5) The cut margin of vesicouterine peritoneum is sutured to the cervical stump and anchored to the vesicocervical pillars of fascia, thus bringing it up under the bladder and the vesicocervical fascia is approximated for its entire length. (6) The vaginal incision is sutured and the anterior stump of amputated cervix is closed by the Sturmdorf technic. (7) Repair of pelvic floor and rectocele is accomplished.

The authors admit the operation is more time-consuming and somewhat more complicated than either the vaginal hysterectomy or the Watkins interposition operation, and caution against its use in poor operative risks. The authors hope others will utilize this operative procedure to help determine its real value.

**Prolapse Following Hysterectomy**—Five cases of prolapse following hysterectomy were seen by Hamilton<sup>58</sup> within a space of two months; three cases were following subtotal hysterectomy, one following vaginal hysterectomy, and the other following total hysterectomy.

In subtotal hysterectomy, the fan-shaped fascia of the cervix is little disturbed, and it would seem that there should be no increase of prolapse following the operation. However, the uterus in its normal anteflexed position prevents prolapse. Following subtotal hysterectomy, the cervical stump may be

aligned with the vagina, thereby favoring prolapse. In addition, it is easier to invert a cylinder than a cone. The presence of the cervical stump keeps the upper vagina open, thus converting the vaginal tube into a cylinder.

In total hysterectomy, the vagina is shortened and the lumen reduced. This conelike effect safeguards against prolapse.

In vaginal hysterectomy, there is usually some repair of the pelvic supports and the vagina.

**Prevention — Subtotal hysterectomy**—The round ligaments should be attached to the cervical stump in such a manner so that the axis of the vagina is not brought into the same alignment as the direction of the intraabdominal pressure.

**Total Hysterectomy**—The vagina should be closed in a lateral-to-lateral manner in order that the lateral ligaments form a more tense sling to the upper vagina.

**Vaginal Hysterectomy**—In addition to support of the broad ligaments, a *perineorrhaphy* should be performed.

In order to obtain good results, the surgical treatment must make coitus difficult or impossible. Therefore, the author advised a radical procedure, a complete *colpectomy* after the manner of LeFort.

### Salpingography

Green-Armytage<sup>59</sup> studied 2000 cases of sterility by hysterosalpingography and pointed out that therapeutic results have not yet been sufficiently appreciated.

A questionnaire to a large consecutive series of patients who had had salpingograms showed that 31 per cent of the patients had conceived and gone to term. He discussed the probable methods of overcoming sterility with salpingograms and stated if the oil be injected imme-

diately after cessation of menstruation, conception frequently occurs within three months.

Hysterosalpingography is also valuable in evaluating the problems of sterility in women after a septic labor or abortion, after appendicitis, extrauterine pregnancy, and the like.

The authors' technic requires collaboration between radiologist and surgeon. The *lipiodol* is injected and watched on the fluoroscopic screen passing from the uterus to the tubes and gently spilling (after 5 to 6 cc. as a rule) into the peritoneal cavity. When a satisfactory picture is featured, the x-ray film is taken.

The author pointed out some of the more common errors in the interpretation of films.

One of the most common errors is to give a hopeless prognosis when the film shows that both cornua are rounded. This happens most frequently when there has been a history of septic labor or criminal abortions. With such a history, only the interstitial portion of the tubes are occluded and the distal portions are usually patent. For such, the author recommends intrauterine tubal transplants.

Should the history suggest gonorrhea and the tubes are blocked just beyond the cornua, surgery is not considered. For blocks involving the fimbriated ends, *salpingostomy* is recommended.

Gynecologists should not give a pessimistic prognosis or conclude that the tubes are occluded merely because they can not be seen on the film, or they have a "dog's ear" appearance at the cornua. This illusion may be due to tubal spasm.

A small hypoplastic uterus with tubes which appear to be long and tortuous does not presage that such a patient cannot become pregnant.

Previous tubercular peritonitis or gangrenous appendicitis may cause retro-

version and the tubes, if patent, have a beaded or rosary appearance.

Fibroids may cause filling defects. Lateral films are of great value in evaluating the prognosis.

### Women in Industry

Hesseltine<sup>60</sup> stresses the lack of medical data on the effect of various kinds of employment on the gynecologic and obstetric future health of unmarried or childless women, on the pregnant, puerperal, or lactating women, or on mothers with home and family responsibilities.

It is a common experience in industry that women absent themselves more frequently from work and for longer periods than men. No facts are available as to how much of this absenteeism is due to obstetrical and gynecological disability.

A good medical service includes a physician with genuine interest in the job, properly trained industrial nurses, cooperation with state and local personnel in improving working environment.

A health program should include:

First aid, emergency, and subsequent medical and surgical care for all industrially induced disability. Correlation with the family physician and other community health agencies for proper management of nonoccupational sickness and injury. Health conservation through periodic examinations and health education. Good record of all causes of absenteeism to assist in prevention of same.

Since many women work at home and since rest at home is difficult during the day, mothers should work either the day or afternoon shifts. Women are particularly suited to work involving manual dexterity. They should not be expected to handle weights beyond 35 pounds and the limit should be less for pregnant and for older women with relaxed pelvic floor or beginning prolapse.

Working garments and equipment should be designed to avoid danger from catching in machinery; should protect against extremes of heat and cold, and should furnish protection for hands, eyes, and hair. Hours of work should be from 36 to 48 a week.

Special rest rooms for menstruating, pregnant, or ill women should be provided, as well as proper standards as to ventilation, lighting, toilet facilities properly maintained and readily available.

Proper supervision of women at work by trained supervisors is necessary.

Transportation may offer special problems of protections and shelters from the transportation system to the factory.

Physical examinations should be complete preplacement, and subsequent examinations complete enough to insure protection. Personal records should be carefully kept in confidence, and the examinee should be acquainted with the results of the examination.

Pregnant and lactating women as well as sterile ones and women subject to habitual abortion should be particularly protected against lead, mercury, phosphorus, arsenic, solvents, benzene and homologues, volatile oils, nitrobenzene and explosives, x-rays and radium, and other dangerous agents. Women with a bad history as regards infertility, toxemia, or habitual abortion should avoid working until the underlying condition has been cured.

Menstrual disorders may cause absenteeism. Severe cases should be treated by a specialist consultant. Moderate cases should be given an opportunity to rest, and have hot applications for a few hours, if necessary, rather than lose full days. For those who must lose time because of dysmenorrhea a make-up period can be arranged of one or two days during the month. Menstrual disorders may be the first sign of cancer. Early diag-

nosis may lead to complete cure in a given employee.

The nervous instability of the menopause may decrease efficiency and may be easily controlled in many cases by estrogenic therapy. Adjustments of the type of employment may be necessary to meet psychic changes or physical defects which may appear at this time.

Each pregnant employee should have individual consideration by her own physician and by the plant physician as to hours, type, and duration of employment. They should have a regular shift so that they gain the maximum rest and sleep. All pregnant women should stop work at the thirty-second week or even the last trimester. The employer should be notified during the first trimester. She should not return to work until six weeks after delivery. This may be extended by advice of her physician if the mother or baby need extra care. All routine antepartum care should be given by a private physician. Complications of pregnancy are best handled by the patient's physician, but emergency service should be handled by the plant physician. Lactation should be permitted and sufficient time granted. Other children in the family must be provided for.

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## OBSTETRICS

ARTHUR FIRST, M.D., F.A.C.S.

### MENSTRUATION

**Treatment of Delayed Menstruation**—A combined method for the treatment of delayed menstruation and a test for early pregnancy is reported by Carapetyan.<sup>1</sup>

Each patient who presented herself for the treatment of delayed menstruation was subjected to a careful history taking and physical examination. After endocrine disorders and organic diseases were ruled out, as many of these women as could arrange it (about 70 per cent of the total) were given a Friedman pregnancy test in order that early pregnancy might be either ruled out or established. All of the pregnancy tests were performed before the administration of the treatment.

Each patient received an injection of 1 mg. ( $\frac{1}{65}$  gr.) of *prostigmine methylsulfate* on three consecutive days. If the menstrual flow was established after the first or second injections, further treatments were deemed unnecessary. If no menstrual flow occurred within 72 hours after the last injection, a tentative diagnosis of pregnancy was made until this state was confirmed by a Friedman test or subsequent clinical observation.

The ages of the patients ranged from 19 to 49. Women who, regardless of their age, had long standing records of irregular menstruation, and those in

whom the amenorrhea was definitely due to an endocrine dysfunction or organic disturbance, were considered unsuitable for treatment. Nevertheless, for the sake of completeness of the study, a number of such cases were included.

In this study of 57 patients prostigmine methylsulfate was used as a therapeutic agent in delayed menstruation and was found to be successful in inducing a normal menstrual flow in all women who were not pregnant.

**Ovulation Time**—Determining the time of ovulation is especially important in patients with varying periods of amenorrhea in whom artificial insemination is contemplated. A comparison of methods used in determining the time of ovulation is presented by D'Amour.<sup>2</sup>

It is now generally accepted that ovulation usually occurs during the midinterval of the menstrual cycle, and that it is under hormonal control. The length of the midinterval, the frequency of non-ovulatory cycles, and whether ovulation may occur more than once in the interval between menstrual cycles is not known.

Four methods are available which depend on ovarian function. These are: (a) Gonadotropin assays, because hypophyseal activity governs ovarian function; (b) estrogen assays, because the ripening follicle produces estrogen; (c) pregnandiol determinations, because its

precursor, progesterin, is formed by the corpus luteum after ovulation; (d) vaginal smears, because the vaginal epithelium is altered in response to ovarian hormones.

Not as strong a case can be made for methods in which the relationship to ovarian function is less clear. Cyclic changes in body temperature, for instance, are more difficult to evaluate, and the same is true of alterations in electric potential and hemoglobin reduction. Subjective experiences are most unreliable of all, because of their vagueness and variety.

The purpose of this study was to compare, on the same 20 cycles, results obtained by six indirect methods for the study of the time of ovulation, namely, gonadotropin assays, estrogen assays, pregnandiol assays, vaginal smears, body temperatures, and subjective experiences.

It was concluded that: (a) Subjective experiences were valueless as tests for ovulation; (b) body temperature fluctuations were not sufficiently regular or clear-cut to be reliable; (c) the uniformity of the results of hormonal assays and vaginal smear confirmed the validity of each and that a certain sequence of events appears typical of the normal cycle; (d) because of its sharpness and its apparent close association with ovulation, the gonadotropin peak occurring in the midinterval was considered as most indicative of the exact time of ovulation.

## ABORTION

### Causes

A working classification of the causes of abortion is presented by Meaker.<sup>3</sup>

Every accomplished abortion includes three events: death of the embryo, separation of the ovum from its attachments, and expulsive uterine contractions. Any one of these may be the primary event

in a given case followed sooner or later by the other two.

**Death of the Ovum**—In some cases of abortion the embryo dies days or even weeks before there is any evidence of ovular detachment in the form of bleeding or of expulsive uterine contractions in the form of cramps. In others the embryo, already moribund, dies after some slight appearance of bleeding or cramps but before these symptoms are well established. In the first the trouble is hereditary. In the second sort of case the trouble is environmental. A normal ovum succumbs after nidation either because of malnutrition from poor implantation or, less often, as a result of acute or chronic disease in the mother.

When constitutional treatment of one or both partners is carried out before the start of pregnancy, it may be assumed that increased fertility in the parents results in the survival of a certain number of embryos which otherwise would not have had enough vitality to complete their intrauterine development.

**Separation of the Ovum**—The commonest initial event in spontaneous abortions is some degree of ovular separation.

There is probably no agent short of instrumental intervention which will bring about the detachment of a normal ovum properly implanted in a normal uterus.

The formation and the maintenance of a normal decidua depends on two factors: adequate endocrine stimulation and a healthy endometrium capable of responding.

**Expulsive Uterine Contractions**—There are several anatomic conditions which make growth of the pregnant uterus beyond a certain point difficult. The hypoplastic uterus is subject to this handicap because of the relatively large amount of connective tissue in its myometrium.

Various external influences evoke contractions in the pregnant uterus. Falls, other bodily injuries, and surgical operations can have this effect. Coitus in some cases undeniably initiates abortion.

**Estrogen** activates the uterine musculature and tends to stimulate contractions; **progesterone** has a sedative or inhibitory effect. Hamblen, however, believes that large doses of progesterone may precipitate abortion by depressing the intrinsic progesterone-pregnandiol metabolism.

The guiding principle of treatment should be the reestablishment of a normal estrogen-progesterone balance with small doses of one or the other hormone as needed. Vaginal smears provide a valuable method of determining the indications.

### Missed Abortion

An analysis of results following conservative management is presented by Lubin and Waltman.<sup>4</sup> The authors analyzed 18 cases where the fetus died before viability was reached and was retained for at least 28 days.

No interference from below was attempted in cases where there was no bleeding and the only indication for surgical intervention was active bleeding. One case required a sponge stick removal of retained secundines after rupture of the membranes and passage of some of the gestational contents. Of the remaining 17 cases, 16 passed the intact sac with the placenta and one ruptured the membranes and then delivered a macerated fetus. In two cases, retained for 17 and 28 weeks, respectively, *stilbestrol* tablets were given in 1 mg. ( $\frac{1}{65}$  gr.) doses daily for four and five days. In the first of these two cases spontaneous expulsion of the entire gestation followed, but in the other case the membranes ruptured spontaneously, after

which bleeding followed and sponge stick removal of the retained secundines was necessary. The remaining 16 cases were followed in the Prenatal Clinic after the diagnosis was made and were treated symptomatically. In some instances medical induction of labor, using castor oil and hot enemas, was attempted without success. Surgical procedures were not attempted.

The theoretical difficulties which might be encountered in surgical evacuation of the uterus, namely, forcible tearing of a nondilatable cervix and bleeding from a noncontractile uterus, the authors feel can be averted by not resorting to interference from below.

No patient, in the series reported, presented alarming symptoms of retention, as toxemia, hemorrhage, or infection.

There was no maternal mortality and in only one case was there any morbidity. The Friedman test was of value only when negative.

Analysis of the series of cases presented justifies a policy of waiting for spontaneous expulsion of the dead ovum in missed abortion. Medical or hormonal trials to induce uterine contractions for the expulsion of the dead ovum may be attempted with safety.

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## PREGNANCY

### Pregnancy Tests

A two- and six-hour pregnancy test has been devised by Kupperman, Greenblatt, and Noback,<sup>5</sup> based on the six-hour test advocated by Salmon *et al.*

The end-point of this test is dependent upon the hyperemic effect of urinary gonadotropin upon the ovarian stroma, corpus luteum, and ovarian capsule. The weight and age of the animal used and end-point employed in this test are as follows: Immature female rats of 21 to 55 days of age may be used for the two-



hour test and female rats of any age are satisfactory for the six-hour test. With reference to their procedure, the authors define an immature rat as one in which neither vaginal introitus nor corpus luteum formation has occurred.

**Two-hour Pregnancy Test**—Immature rats, as defined above, are injected intraperitoneally with 1.5 cc. of a morning sample of the urine. Divided doses of  $\frac{3}{4}$  cc. are injected into both the right and left lower abdominal quadrants. The animal is killed with ether two hours after injection of the urine and the appearance of the ovary and the ovarian capsule is noted. Hyperemia, as indicated by the reddish appearance of the ovary and capsule, is considered a positive reaction. Until one is able to distinguish between the normal appearance of the ovary which is white or pinkish in color and that of the ovary stimulated by pregnancy urine it is advisable to kill an uninjected animal (litter mate preferred) at the same time as the test animal so that a comparison may be made.

**Six-hour Pregnancy Test with Immature Rats**—Two cubic centimeters of urine are administered by subcutaneous injection and the animal is killed six hours later. The end-point is similar to that observed for the two-hour test.

**Six-hour Pregnancy Test with Adult Rat**—Before the urine is administered vaginal smears are taken and only those animals in metestrus or diestrus are used. Five cubic centimeters of urine are injected subcutaneously and the animal is killed six hours later. The recent corpora lutea of animals injected with pregnancy urine appear dark red to purple in color, and microscopically they show a marked degree of vascularization. Here again it is suggested that until one becomes adept in reading the tests, control animals in the same stage of the cycle should be killed, simultaneously, for

comparison with the rats injected with urine. As an aid in reading these tests, the authors have found that a more definite reaction is observed two to three minutes after the animal has been killed and the viscera exposed for inspection. In addition, the reaction of the corpora lutea of the adult animals may be more easily interpreted when the ovaries are placed in formalin. The control ovaries and corpora lutea remain pale in color, while those from animals injected with pregnancy urine turn dark brown or a decidedly darker shade than the controls after being placed in formalin. By means of this simple procedure a convenient set of standards may be prepared and kept indefinitely for comparison with the results obtained from unknown samples of urine.

Of 33 specimens of urine from non-pregnant individuals, there was no instance of a false positive reaction. Only two of 48 samples of pregnancy urine gave an indecisive reaction, but the urines from these patients yielded strongly positive reactions five days later. In performing the test three rats are sufficient, two for the two-hour test and one for the six-hour test. However, if necessary only one animal may be used if the test is positive, but in instances of a negative test it is advisable to inject at least two more animals for confirmatory data.

### Length of Pregnancy

Pregnancy actually begins the moment the female egg cell becomes fertilized and ends with the birth of the child.<sup>6</sup> The time estimated as the length of pregnancy is difficult to determine on account of several variable factors: (1) The question of the time of ovulation; (2) the time of migration; (3) the lifetime of the egg and the spermatozoa; (4) the time of impregnation, and (5) the time of implantation of the ovum.

The longest possible period of gestation has not been legally defined in this country. French law recognizes the legitimacy of a child born 180 days after marriage and 300 days after the death of the husband, the German law 181 and 302 days, respectively. In England in 1921 the legitimacy of a child born 331 days after the husband went to war was allowed. In the United States each case is decided on its own merits, since there is no law in this country or in England which defines the duration of gestation.

The problem is further complicated by the fact that there are no accurate criteria for ascertaining the degree of hypermaturity of newborn infants; even fully formed teeth are sometimes found in those born at term.

For practical purposes the burden of proving any pregnancy lasting more than 280 days would seem to rest on the claimant.

### Pregnancy Complications

**Syphilis—Treatment by the Five-Day Massive Dose Method** — The treatment of 27 cases of syphilis in pregnancy by the five-day massive dose method is reported by Rattner.<sup>7</sup>

A daily dose is given of 240 mg. (4 gr.) of *mapharsen* dissolved in 2000 cc. of 5 per cent glucose solution administered by intravenous drip on each of five consecutive days. The treatment was well tolerated by both mother and fetus, regardless of the stage of the pregnancy or the duration of the syphilis, whether primary, secondary, or latent. In no instance was there encountered a severe reaction or interference with the pregnancy.

Of the 27 cases, one was lost from observation; 25 have resulted in the birth of full-term, normal infants, and one syphilitic infant was born of a mother who apparently had acquired a second in-

fection while the infant was still *in utero*. In addition to this group, five other patients who had been treated for early syphilis by the massive dose method later became pregnant and gave birth to normally developed, seronegative infants, although further antisyphilitic treatment was purposely withheld from the mothers.

**Hydatidiform Mole**—The problem of what course to pursue in the presence of a persistent positive test following the passage of a mole, an abortion, or term pregnancy is discussed by Williams.<sup>8</sup> It is his custom in the presence of a persistent positive test to perform a curettage and, if a month or so later the test is still positive, an abdominal exploration of the pelvis with hysterectomy is advisable.

A discussion of hydatidiform moles and their subsequent course, with a review of 24 cases, is presented. The mole may be benign, its passage complete, and recovery may be uneventful. In others, approximately one-half of the cases, chorionic tissues remain in the uterine cavity or in the uterine walls, and cause persistent positive biologic pregnancy tests.

The author classifies these cases microscopically as syncytial endometritis or syncytioma (infiltration with syncytium only), malignant mole or chorioadenoma (syncytium, Langhans' cells, and villi), or chorionepithelioma (Langhans' cells and syncytium).

Those diagnosed on this basis as chorionepithelioma have died, while all of the others have survived.

**Toxemia** — Hypertensive toxemia of pregnancy is the basis of a study by Dexter, Weiss, Haynes, and Sise.<sup>9</sup> This study is based on observations of: (1) 100 normal pregnant women; (2) 100 patients who presented generalized edema uncomplicated by hypertension during

pregnancy, and (3) 80 patients with hypertension during pregnancy.

Generalized edema is demonstrated in about 75 per cent of all otherwise normal pregnant women. In the absence of hypertension it is seldom of serious pathologic significance. When this generalized edema is associated with hypertension during pregnancy, it assumes exceeding importance.

Approximately 6 to 9 per cent of normal patients have either hypertension or albuminuria, or both, in the latter half (not in the first half) of pregnancy, and these changes are almost always associated with the development of generalized edema.

Patients with prepregnant hypertension of any degree of severity and due to any cause (chronic pyelonephritis, chronic glomerulonephritis, "essential" hypertension, and the like) may have an uncomplicated course during pregnancy, a condition which the authors referred to as "hypertension uninfluenced by pregnancy." Twenty of the 39 patients who had hypertension or albuminuria before pregnancy failed to have a further increase in blood pressure or albuminuria during pregnancy, despite the appearance of generalized edema in two-thirds of the patients. Although the mother fares well, there is a high incidence of miscarriages and stillbirths in this group.

The remaining number (approximately 50 per cent) of the patients with hypertension which antedated pregnancy developed toxemia of pregnancy. From a clinical, pathologic, and laboratory standpoint, this vascular syndrome which was superimposed on a previous hypertension is indistinguishable from the preeclampsia and the eclampsia occurring in patients whose blood pressure and urine were normal before pregnancy.

Elevation of blood pressure and albuminuria do not, therefore, necessarily

indicate that toxemia is present. Toxemia of pregnancy is an acute vascular entity resembling closely acute glomerulonephritis in its clinical characteristics. The most important factors predisposing to the development of toxemia are hypertensive vascular disease of any cause or any degree of severity and the generalized edema of pregnancy. Generalized edema in pregnancy is usually unaccompanied by toxemia. The onset of toxemia, however, is nearly always characterized by the development of edema or its accentuation. The authors emphasize that the basis of therapy of toxemia of pregnancy rests on elimination of this retained fluid. Without diuresis, improvement rarely takes place.

Toxemia is peculiar to the second half of pregnancy, the average time of onset in these patients being at the thirty-fourth week. Blood uric acid is frequently elevated in the mild and almost always in the severe cases.

The significance of albumin in the urine has been emphasized. Addis counts reveal a slight increase in the number of erythrocytes, white cells, and cases of all sorts.

A high incidence of spontaneous prematurity, stillbirths, and neonatal deaths occurs in toxemia of pregnancy. Provided the fetus successfully survived the neonatal period, there were no demonstrable ill effects later from preeclampsia and eclampsia. Approximately 25 per cent of those with normal prepregnant blood pressure who develop toxemia during pregnancy are left with a permanent postpartum hypertension.

Although after a toxemic pregnancy hypertension and albuminuria usually disappear within a few days or a few weeks, they may persist for as long as a year and then disappear permanently.

The earliest changes in toxemia occur in the kidney rather than in the liver.

Renal lesions are diffuse and are primarily degenerative in character.

**Treatment**—The treatment of toxemia of pregnancy is prophylactic and therapeutic. With the appearance of edema, more than the usual supervision should be given even though in most cases it is by itself innocuous. The edema is preventable in many instances by *maintaining adequate nutrition* with a diet containing 100 Gm. or more of protein, a low value of salt, a high carbohydrate level, and a caloric value of about 2000. The diet should include lean meats and eggs with abundant fruits and vegetables. Fats, with the exception of a moderate amount of butter, should be eliminated. When patients adhere to a diet of low salt content there is no need to restrict fluid intake. *Sodium bicarbonate* and *sodium-containing preparations* should not be used for heartburn. Preparations devoid of sodium, such as *magma magnesiae* or "*amphojel*," should be prescribed in the treatment of this symptom. In the more resistant cases, diuretics are employed. *Potassium chloride* in 2 Gm. (30 gr.) doses three to four times a day, *ammonium chloride* in 1 Gm. (15 gr.) capsules six times a day for three days and repeated after an interval of three days, or *magnesium sulfate* 8 Gm. (120 gr.) daily by mouth may be beneficial in promoting loss of edema. If the edema is pronounced and symptoms exist, the patient should be put to bed for seven to ten days and placed on a *1200 to 1500 calory diet* composed mainly of fruit juices, sugar, and skim milk.

**Treatment of Preeclampsia** — Aside from bed rest and sedation for adverse symptoms, practically all effective therapy in preeclampsia (and eclampsia) consists in producing water elimination, whether by purges, restriction of salt and sodium bicarbonate in the diet, admin-

istration of diuretics or, finally, evacuation of the uterus. Should the hypertension and albuminuria, even if slight, persist for a period of four weeks, the authors advocate considering termination of pregnancy as a safeguard against the development of permanent postpartum hypertension or albuminuria.

**Treatment of Eclampsia**—The most reliable sign of improvement is diuresis, and until diuresis occurs improvement rarely takes place. For this reason, an indwelling catheter with a two-hourly recording of urinary output is serviceable.

Diuresis may be aided and abetted by the slow administration intravenously of 50 cc. (2 fl. oz.) of *50 per cent dextrose*. Transfusion or administration of *concentrated protein solutions* is the most important measure for promoting diuresis. It must be given slowly (500 cc. [17 fl. oz.] in two to three hours) with the patient in the orthopnea position in order to avoid pulmonary congestion.

Although an extreme hypertension in eclampsia is of danger to the patient, the authors claim that the earliest sign of impending disaster is almost always an insidious, progressive fall in arterial blood pressure terminating in shock and death. This fall in blood pressure is often due in part to excessive use of sedatives, in part to indiscriminate blood letting, and in part to the disintegration of the body as a result of the disease. Venesection should be reserved for pulmonary edema alone. Should the blood pressure fall to hypotensive levels, transfusion or administration of concentrated protein solutions is the most important measure for checking the progress of circulatory collapse.

The method by which pregnancy is terminated depends on many factors. If the cervix is "ripe," labor can usually be successfully induced by rupture of the membranes or insertion of a bag. Ec-

lambtic patients are not good anesthetic risks. The authors favor as the most satisfactory therapy the so-called middle course treatment which condemns routine accouchement forcé and cesarean section and which advocates improving the general condition and carrying the patient along until spontaneous delivery or delivery enhanced by dilatation of the cervix is feasible.

**Edema of Pregnancy**—The relationship of the estrogens and progesterone to the edema of normal and toxemic pregnancy is discussed by Taylor, Warner, and Welsh.<sup>10</sup>

The retention of sodium and water during pregnancy, the authors believe, is due to the estrogenic material produced by the placenta and its loss during the puerperium to the disappearance of the estrogens. In the present study, the relationship has been further investigated by the administration of large doses of these substances during pregnancy and the puerperium.

The retention of water in normal pregnancy is indicated by the degree of weight gain, by the frequent slight edema of the lower extremities, by an increase in the volume of plasma and of extracellular water. The rise in plasma volume is manifested by an increased water content of the blood, a reduction of red cell count, hemoglobin, hematocrit, and plasma proteins.

The retention of sodium parallels that of water, for a consistently positive balance, for this ion has been shown to exist during the latter months of pregnancy. A part of the positive sodium balance can be attributed to the needs of the developing maternal and fetal tissues, but there is in addition an altered capacity of the pregnant woman to eliminate sodium. This is shown in the retention of relatively large proportions of administered sodium chloride, and in the de-

layed elimination of measured quantities of ingested water.

With parturition changes in these relationships set in. During labor and immediately afterwards, the blood becomes more concentrated. This is in part due to blood loss, partly to the effects of muscular effort and dehydration, and perhaps in part to a redistribution of water as a result of the disappearance of the placental circulation. This period of blood concentration is of short duration, however, for within 48 hours the plasma volume again rises and immediately thereafter diuresis commences. Large quantities of sodium appear in the urine the next few days and there is a considerable loss of available extracellular water. The secondary expansion in the plasma volume after delivery may be attributed to the return of the excessive quantities of interstitial fluid to the vascular stream. This in turn leads to the diuresis of the early puerperium.

It was hoped that by administering large quantities of the *estrogens* and *progesterone* in the puerperium, concentrations of these substances characteristic of pregnancy might be maintained.

Five patients received hormones, either estrogen or progesterone, immediately after delivery in an effort to prevent or modify the sodium loss and diuresis of the early puerperium. In three of these patients large doses of hormones were also given during pregnancy to determine whether the sodium balance was in any way disturbed by such treatment.

The absence of the postpartum sodium loss in one and its apparent reduction in another case of normal pregnancy after estrogen treatment in the puerperium is additional evidence that one of the causes of sodium and water retention in normal pregnancy is the high estrogen concentration characteristic of the body fluids during that period. That proges-

terone may contribute to this is suggested by the case treated by this substance in which the loss of sodium in the early puerperium was relatively slight. The effect of estrogens and progesterone in preventing diuresis and sodium loss in the puerperium of patients who had had toxemia of pregnancy was less convincing but still suggestive.

**Diabetes** — Pregnancy complicating diabetes was investigated by White and Hunt.<sup>11</sup> Between 1922 and 1939, only 62 per cent of the 228 pregnant diabetic women at their clinic delivered viable infants; 15 per cent of the total number of pregnancies terminating in abortion or miscarriage, 23 per cent in stillbirths or neonatal deaths. Because this was essentially the same percentage as that recorded for pregnant diabetic patients *prior* to the discovery of insulin, an investigation of the hormone excretion levels in such cases was undertaken.

One hundred and nineteen diabetic patients were studied after the twenty-fourth week of pregnancy in order to determine hormone excretion values for gonadotropin and pregnandiol. Fifty-one (42 per cent) developed toxemia (hypertension and/or albuminuria otherwise unexplained) and 25 (20 per cent) delivered before the thirty-sixth week.

Acidosis, *per se*, is not important as a lethal factor in producing fetal death, as is shown by the increase of only 6 per cent in the fetal survival rate following the inauguration of insulin treatment. The authors have not seen cases in which maternal hypoglycemia has contributed to fetal death.

Whether or not the placenta is permeable to insulin has not been clearly established.

Theoretically, placental glycopenia may result from uncontrolled diabetes or more probably from the reverse condition, hypoglycemia, whereby there is a blockage

of glycogen in the placental cells leading to glycogen insufficiency.

The authors conclude that defective ova or disturbed chemistry of diabetes does not seem to explain adequately the fetal wastage and abnormal clinical course of diabetic pregnancies. The hormone study was therefore undertaken.

One hundred and twenty-five consecutive cases of pregnancy complicating diabetes were classified as having a normal or abnormal balance of the hormones in pregnancy, based on results of chorionic gonadotropin assays in all cases and on pregnandiol determinations in 60 cases.

In 41 cases the hormonal balance was normal, in 77 abnormal. The first 27 cases of abnormal hormonal balance received no hormonal therapy except insulin.

Fifty cases were classified as having abnormal hormonal balance and were treated. Forty-four had a well-established abnormal rise in the level of chorionic gonadotropin during the twenty-fifth through the thirty-third week. Six were included largely because of low pregnandiol excretion values.

Among the 41 pregnancies in which the hormonal balance was normal, spontaneous premature delivery before the thirty-sixth week did not occur. Fetal survival was 95 per cent for the 41 cases.

Total fetal survival in the 27 cases of abnormal hormonal balance which were untreated was 60 per cent. Therapy was attempted with *estrogens* and *progesterone* in 50 cases of this group in which there was known hormonal imbalance and in seven additional cases which were included, two on the basis of history and five on the basis of symptoms, a total of 57 in the group of treated patients.

Fetal survival for the 57 was 92 per cent, and for the 50 in which treatment

was indicated by the result of hormone assays it was 90 per cent.

**Treatment** — The management of pregnancy in diabetes may be divided into three parts: (a) Hormonal; (b) diabetic, and (c) obstetric.

**Hormonal Treatment**—If the pregnandiol level falls below the normal according to the curve of Venning and Browne, **progesterone** therapy is instituted. If the results of two tests, preferably consecutive, during the critical period from the twenty-fifth through the thirty-third week show a rise of 200 or more R. U. of chorionic gonadotropin per 100 cc. of blood, therapy combining **estrogen** and **progesterone** or a **progestin-like substance** is started.

The dosage was varied and was not less than 5 mg. ( $\frac{1}{13}$  gr.). In some instances it was as high as 50 mg. ( $\frac{10}{13}$  gr.) per day. Estrogen therapy likewise was maintained daily from the time of its initiation to delivery. The daily dosage for **stilbestrol** ranged from 10 to 50 mg. ( $\frac{2}{13}$  to  $\frac{10}{13}$  gr.) parenterally and from 40 to 120 mg. ( $\frac{4}{13}$  to 2 gr.) orally. Most of the patients required 120 mg. (2 gr.) orally. Nausea and vomiting as a result of this dosage did not occur.

Patients receiving large doses of stilbestrol for five days postpartum or two days longer than would be usual for surgical delivery also receive **intravenous glucose** twice daily.

**Diabetic Management**—Diabetic management of patients during pregnancy is not difficult. The diet must be adequate. Calories are prescribed by weight, namely, 30 per kg. of increasing body weight. The carbohydrate allowance is liberal, 200 Gm. The protein intake should be high, 2 Gm. per kg. of body weight, and sufficient fat to complete the caloric requirement.

The diet is supplemented with vitamins, including **vitamin E**, which is

given early in pregnancy, and **vitamin K** which is given later in anticipation of delivery. The use of **sodium bicarbonate** is prohibited and the **sodium chloride** intake is reduced after the sixth month.

**Insulin** is prescribed primarily according to blood sugar levels rather than urinary sugars in order to avoid the pitfalls resulting from the lowered renal threshold. The usual routine for treatment with insulin in their clinic is simultaneous administration of **protamine zinc insulin** and **crystalline insulin** before breakfast.

A pregnant diabetic has the same prescription based on blood sugar levels, but, in addition, small to larger doses of insulin are given before lunch and the evening meal. The amount of insulin for the small later doses is determined by the result of urinary rather than blood sugar tests. These small doses prevent the excretion of glucose, which is often excessive in pregnancies, amounting to as much as 50 to 100 Gm. daily even when the blood sugar levels are nearly normal.

**Obstetrical Management** — Gigantism, breech presentation, and sterilization are indications for cesarean section. In this series of 125 cases, the number of normal deliveries was 46; that by cesarean section, 79.

If cesarean section is performed, no preliminary sedation is administered. **Spinal anesthesia** is the one of choice and **oxygen** is given during the operation. If normal delivery is feasible, **glucose** and **insulin** are given as indicated. According to the course of labor, minimum sedation is prescribed, not more than **nembutal**, 0.194 Gm. (3 gr.), and **scopolamine**, 0.0004 Gm. ( $\frac{1}{150}$  gr.). Spinal anesthesia or nitrous oxide inhalation may be used during the third stage of labor and for episiotomy.



Diabetes is not considered an indication for therapeutic abortion. These 125 pregnancies resulted in 108 living babies and 124 living mothers. Autopsies were performed on 15 of the 17 fatal cases. All of the infants that died exceeded the expected weight for age.

Hypoglycemia, to which the low rate of fetal survival in diabetics has often been attributed, has not been lethal in the authors' experience. The blood sugar in infants of diabetic mothers often falls from birth level in four hours with a spontaneous rise without the administration of glucose or oral feeding, usually within eight hours. The lowest blood sugar, 9 mg. per cent, was associated with signs of hypoglycemia. Glucose relieved the infant instantly.

The most favorable effects of hormone therapy to the mother appeared to be upon weight, edema, and hydramnios. With hormonal treatment, hypertension and albuminuria appeared to be modified and serum protein levels tended to rise. The significant progression of hypertension and albuminuria was exceptional when adequate hormonal treatment was inaugurated sufficiently early.

**Fibroids**—To determine whether the old clinical observation that uterine fibroids enlarge during pregnancy is true, Randall and Odell<sup>12</sup> studied 17 cases of uterine fibroids removed in the presence of pregnancy.

Degenerative changes of some degree were present microscopically in 10 of the 17 cases. There was no evidence of hypertrophy of the muscle fibers within the fibroids and no hyperplasia of the connective tissue cells as evidenced by unusual mitotic activity. Significant edema could be seen in only one of the fibroids. None of the fibroids showed any increase in the size and number of blood vessels when compared to fibroids removed from nonpregnant patients.

The authors conclude that approximately 50 to 75 per cent of all fibroids during pregnancy show degenerative changes. Probably most fibroids during pregnancy have a poor blood supply and show little actual growth. Edema on the basis of severe degenerative changes could explain the enlargement of fibroids during pregnancy. However, this enlargement should be accompanied by symptoms. Any suspected enlargement of asymptomatic fibroids during pregnancy is only apparent, the authors feel.

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## CAUDAL ANESTHESIA

### Continuous Caudal Analgesia

A comprehensive analysis of the first ten thousand confinements thus managed with the report of the authors' first thousand cases is presented by Hingson and Edwards.<sup>13</sup>

Thus far from the literature there have been reported three important methods of administration of continuous caudal analgesia:

1. The malleable needle technic with the closed circuit apparatus.
2. The ureteral catheter technic with both closed and broken circuit apparatus.
3. The continuous drip caudal analgesia technic with the closed gravity apparatus.

The special malleable needle technic with the closed apparatus has been used by the authors in 1000 of their cases. Of the 10,000 cases reported, this technic has been used in 6400 cases. This is the technic of fractional dosage in which an initial dose of 30 cc. of 1.5 per cent **metycaine** is used, as soon as the labor has been definitely established, to relieve subjective pain. Supplementary doses are injected at intervals varying from 40 minutes to an hour and a half.

Hingson and Edwards prefer a 1.5 per cent solution of metycaine in isotonic

solution of sodium chloride because of: (1) The high analgesic efficiency of the drug; (2) the reduced number of reactions that could be ascribed to the drug, and (3) the rapid elimination of the drug with a quick recovery of nerve impulses and physiologic control after delivery.

The authors state that the anatomic proximity of the sacral hiatus to the nerves of the pelvis, perineum, and the lower extremities makes this method applicable to all types of obstetric and gynecologic procedures. The peridural space surrounding the dura mater as a sleeve from the foramen magnum to the hiatus sacralis comprises the area between the dura mater and the periosteum lining the spinal canal but usually at the second sacral segment communication between these two parts is interrupted by the closure of the dura mater around the nerve trunks. In dissection of cadavers they found that the dura sometimes encircles the spinal nerves of the cauda equina and the filum terminale, with its distal sac extending no farther down the vertebral column than the fifth lumbar segment. In approximately 0.5 of 1 per cent it extends all the way to the fourth or fifth sacral segment. In these instances spinal fluid can be obtained by inserting a short needle through the sacral hiatus. While this phenomenon has been observed by one of the authors in only nine in 2000 caudal injections, the occurrence of anomalies and malformations of the vertebral and spinal canals should be kept in mind.

On the outer surface of the dura in the epidural space, especially at the sides, are extensive venous plexuses which may be penetrated with the caudal needle. The operator should attempt to direct this needle always in the midline and just under the bony roof of the sacral canal in order to minimize this hazard.

The sacral canal terminates below in the hiatus sacralis, forming a triangular opening the sides of which are marked by bony ridges known as the sacral cornua. This opening varies in different individuals. It may be abnormally large, owing to a deficiency in one or more of the vertebral arches, or it may be reduced even to the extent of complete obliteration by ossification.

**Malleable Needle Technic as Recommended by Authors**—1. The patient is placed in the modified left lateral Sims position. The sacral and coccygeal area is cleansed with ether and prepared with one of the antiseptic tinctures.

2. The tip of the coccyx is palpated with the middle finger of the left hand, and the thumb is used to find the U- or V-shaped notch indicating the sacral hiatus between the sacral cornua. This is usually about  $1\frac{1}{2}$  or 2 inches from the tip of the coccyx. In cases in which there was a failure of the inferior sacral arches to fuse into the bony roof of the sacrum, this hiatus may be  $2\frac{1}{2}$  to 4 inches from the inferior caudal tip. Experience with the standard single caudal injections is a desired prerequisite for the success in the use of the continuous method.

3. The middle finger of the left hand then changes place with the thumb and marks the spot for raising the initial skin wheal.

4. A special apparatus has been developed for this procedure. The analgesic agent recommended by the authors is 1.5 per cent *metycaine in isotonic solution of sodium chloride*. Two grams (30 gr.) of the drug diluted in approximately 125 cc. of saline solution in the reservoir bottle will most nearly approach this concentration. With a few cubic centimeters of this solution, skin anesthesia is obtained by raising a skin wheal with a 25 gauge, and deeper infil-

tration to the sacrococcygeal ligament with a 2 inch 22 gauge needle.

5. The special malleable stainless steel 19 gauge needle is then inserted in the midline in the direction of the hiatus at about a 45 degree angle with the skin.

6. As soon as the bevel of the needle pierces the sacrococcygeal ligament, its reinforced metal collar is depressed through an arc of 1 to 3 cm. and the needle is thrust slowly and evenly in the midline for one to two inches within the sacral canal, where its bevel should lie inferior to the lowest extent of the dural sac. This may be ascertained by measuring on the skin with the stilet the approximate extent of the needle. The point of the needle should always be below the level of the second sacral spine.

7. The small section of tubing with special adapter is then slipped over the collar of the needle. The Luer-Lok syringe is securely attached to the adapter. A careful aspiration is performed.

(a) Should clear spinal fluid be obtained, the needle has pierced the dura and lies within the subarachnoid space. In such event the needle should be immediately withdrawn and the case ruled unsuited for caudal analgesia for fear of producing a massive spinal injection of the analgesic drug. Anatomic anomalies with such low lying dura are rare. (In the authors' experience this has happened only twice in more than 1000 injections.) A failure to recognize this situation would be extremely hazardous, if not fatal.

(b) The withdrawal of pure blood indicates that the needle has pierced a small blood vessel in the highly vascular peridural space. In this event the point of the needle should be moved until blood can no longer be obtained. Then the injection is continued cautiously.

8. The danger of intraspinal injections, with appearance of spinal fluid,

can be minimized if a trial dose of 8 cc. of the solution is injected and further action delayed for ten minutes to see that a low spinal anesthesia does not ensue. Without relief of pain or loss of motor power in the lower extremities in ten minutes after injection, one can safely assume that the subarachnoid space was not entered.

9. After these precautions have been carried out, the hose end of the special four-foot rubber tubing is secured over the collar of the special caudal needle. The tubing should previously have been connected to the remainder of the apparatus, all air having been expelled by filling the entire system with metycaine solution.

10. With the palm of the left hand firmly pressed over the skin area against the dorsum of the sacrum, 30 cc. of 1.5 per cent solution are slowly injected.

11. Five per cent *sulfathiazole ointment* is then generously spread around the collar of the needle.

**Indications That the Solution Is Being Injected Into the Peridural Space of the Sacral Canal**—(a) The patients usually experience a sense of fullness, progressing to an uncomfortable sensation in one or both legs as the solution circumscribes the perineural components of the sciatic nerves. This sensation can be minimized by slower injections.

(b) There will be a progressive analgesia in the areas supplied by the coccygeal, hemorrhoidal, perineal, pudendal, ilioinguinal, and iliohypogastric nerve. Analgesia should be complete in 20 minutes.

(c) There is relief of abdominal uterine cramps within 5 to 15 minutes after injection.

(d) Pronounced vasodilatation, cessation of sweating, and increase in temperature of the skin of the feet will ensue within 5 to 15 minutes after injection. This phenomenon is often noticed on one side several minutes before it occurs on the other.

**Indications That the Solution Is Being Injected Outside the Sacral Canal**—(a) Failure of the injection to relieve pain within 30 minutes. (b) The appearance of an "injec-

tion tumor" superficial to the dorsum of the sacrum.

12. *Supplementary Injections*—The supplementary injection will depend on the rate of metabolism of the drug by the individual patient. In their experience 20 cc. of additional solution injected every 30 to 40 minutes is sufficient to keep the parturient comfortable for the entire course of labor. They have continued supplementary injections for a maximum of 30 hours and for an average of seven hours.

There are certain obstetric conditions which indicate the use of continuous caudal analgesia for both the mother and the child.

1. Premature babies.
2. Heart diseases.
3. Use in eclampsia.
4. Use in cesarean section.

**Complications Associated with Continuous Caudal Analgesia**—1. *Broken Needles*—Since the development of their malleable stainless steel needle through a special annealing process, and since they have advocated the use of each needle in only five labors and deliveries, the authors have had no needle breakage in the last thousand cases.

2. *Infection*—In their series of 1150 cases the authors have had one death from a peridural infection at the level of the fifth lumbar and first sacral segment from which a pure culture of staphylococcus was isolated postmortem. This was the identical organism that was found in the blood cultures of the patient several days before death. Death occurred on the thirty-first hospital day. In addition, three minor infections of the sacral and gluteal area occurred with cellulitis and abscess formation.

The following measures should be instituted in all cases of infection in the

peridural space following continuous caudal analgesia:

(a) A repeat caudal insertion should be made with an 18-gauge stiff needle in an attempt to aspirate pyogenic exudate.

(b) Forty cc. of saline solution, containing 75,000 units of *penicillin*, should be made over the dorsum of the sacrum and a soft rubber tube drain inserted through the first or second posterior sacral foramen. A caudal needle should be inserted and a lavage with 5 per cent *sulfathiazole* should be performed every hour for 12 hours.

(c) *Sulfathiazole* or *sulfanilamide* in adequate doses by mouth should be instituted in cases of incomplete relief with *penicillin* and in cases in which penicillin is not available.

3. *Unilateral Analgesia*—This condition occurs in 5 per cent of the cases managed by the needle technic of continuous caudal analgesia in which the patient remains on her side.

The dependent side is usually the one in which the patient has complete relief, and this may be explained by the gravitation of the analgesic solution through the foramina along the nerve trunks on this side. The following measures may be instituted to relieve this complaint:

(a) A subsequent injection of an additional 20 to 30 cc. of the solution may be given and the patient turned to the opposite side immediately thereafter.

(b) In some instances rotation of the needle within the canal toward the side on which the patient complains of pain will more accurately distribute the metycaine in the area where it is needed.

4. *Backache*—This complication was prevalent in about 20 per cent of the first hundred patients, who spent all of their time in labor on their backs. With the patients on their sides, 5 per cent complain of some backache, and a few of these also have an associated pain in the neck incident to subsequent injections.

5. *Convulsions*—There have been only 2 instances of convulsions. One patient had had 3 cc. injected unintentionally.

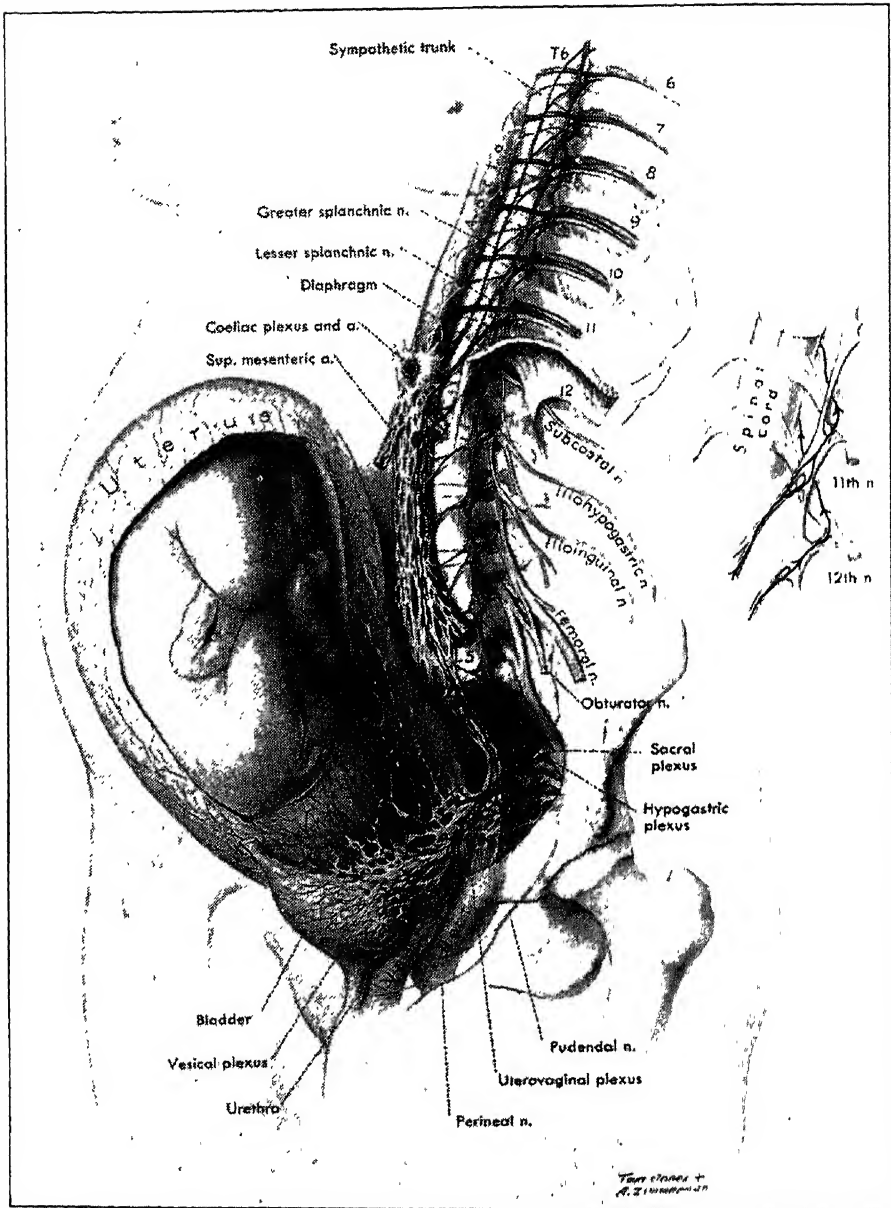


Fig. 1—The innervation of the uterus and birth canal in pregnancy: The sensory nerve fibers of the uterus constitute visceral afferent fibers and are functionally independent of the autonomic nervous system although coursing through the pelvic, hypogastric, and aortic plexuses before connecting with the dorsal root ganglions of the eleventh and twelfth thoracic nerves in which their nerve cells are located. The inset shows details of the connections. The sensory supply to the cervix and upper part of the vagina travels in the sacral parasympathetic nerves. It is also functionally independent of the autonomic system. The sensory and motor supply of the lower vagina, perineum, and pelvic floor travels in the perineal and pudendal somatic nerves. The motor supply of the uterus is autonomic and involves both sympathetic and parasympathetic efferent components. Clinical evidence indicates that the motor fibers to the uterus leave the spinal cord at higher levels than the tenth thoracic nerve, whence they pass through the aortic, hypogastric, and pelvic plexuses. Visceral efferent fibers believed to be motor to the circular muscle of the lower uterine segment and cervix and possibly inhibitory to the remainder of the uterus travel through the parasympathetic pelvic nerves. Clinical study verifies that (1) blocking the sacral nerve roots abolishes the pain of distention of the birth canal, paralyzes the skeletal muscle of the perineum, and abolishes tone in the smooth muscle of the cervix; and (2) extending the block to include the eleventh thoracic root abolishes the pain of uterine contractions without impairing their force. It suggests that extending the block to the sixth thoracic nerve or higher may impair the strength of uterine contractions. (R. A. Hingson and W. B. Edwards: J. A. M. A.)

tionally into the blood vessel. The second patient had 3 Gm. (45 gr.) of 6 per cent metycaine in 50 cc. of solution injected by mistake at a single dose.

**Contraindications**—1. Infection over the site of the area to be injected.

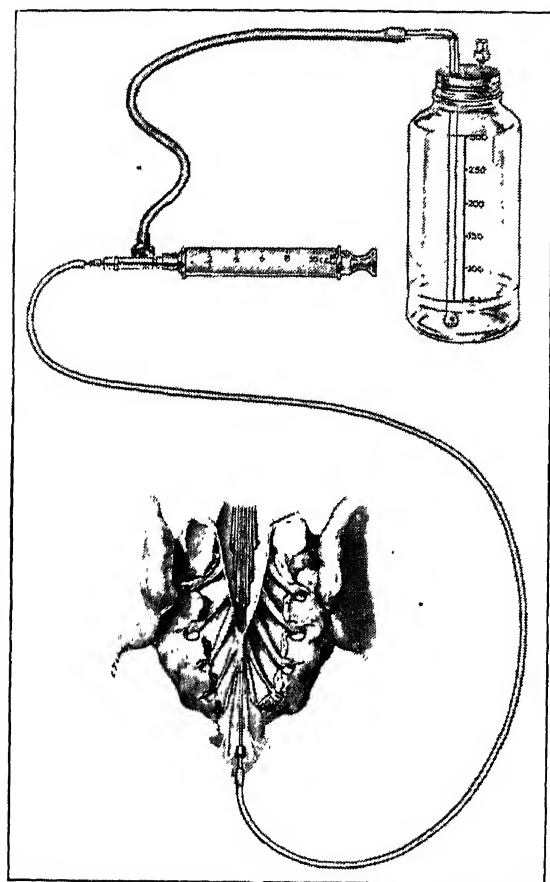


Fig. 2—Apparatus and method of injection into the sacral area. (R. A. Hingson and W. B. Edwards: J. A. M. A.)

2. (a) Anatomic anomalies of the sacrum or bony obliteration of the sacral hiatus. (This is a very rare condition which occurs less than once in 200 cases.) (b) A low lying dura mater in which spinal fluid may be aspirated through the caudal needle. This is an absolute contraindication.

3. Patients with a history of sensitivity to one of the cocaine derivatives or substitutes.

4. Patients with advanced anemia unless the procedure is to be supplemented

with the periodic or continuous administration of a high concentration of oxygen.

5. The psychically unsuited.

6. Cases of placenta previa, unless cesarean section under this form of analgesia is contemplated immediately after its institution. The cervix and lower uterine segment in these cases will become very much softened, thereby increasing the possibility of hemorrhage.

7. Cases of bony disproportion.

8. Extremely obese persons.

From their experience and the accumulated experience of others Hingson and Edwards believe that the following postulates should be emphasized by all obstetricians who use this method:

1. The incidence of operative obstetrics is increased. No physician should use continuous caudal analgesia unless he is well trained in the use of forceps.

2. The incidence of posterior positions is increased to about 8 per cent because of the relaxation of the levator muscles with the resultant failure of a large number of the fetuses to rotate spontaneously.

3. The incidence of transverse arrest in the midpelvis is slightly increased because of the failure of the patient to use her auxiliary expulsive forces.

4. In the hands of the experienced, to offset the first three disadvantages, all types of operative obstetrics are facilitated because of the relaxation of the cervix, lower uterine segment, and perineum. This relaxed state is not achieved by any other form of general anesthesia.

5. No oxytocic drug should be given until after the termination of the third stage of labor, because the uterus in every instance after continuous caudal analgesia contracts firmly with the delivery of the baby. Hemorrhage during the third stage is therefore definitely minimized. Gentle, constant pressure on the fundus of the uterus as the placenta

TABLE I  
ADVANTAGES AND DISADVANTAGES OF ALL TECHNIQS CURRENTLY ADVOCATED

<i>Technic</i>	<i>Chief Advantages</i>	<i>Chief Disadvantages</i>
Malleable needle technic, as introduced by Hingson and Edwards, and used by Gready and Hasseltine.	<ol style="list-style-type: none"> <li>1. Simplicity and safety of needle insertion and drug administration.</li> <li>2. Minimum of trauma to peridural space.</li> <li>3. Accurate control of all subsequent dosage, so that each case may be individualized according to metabolism of drug by patient.</li> <li>4. Possibility of infection reduced through maintaining a closed apparatus throughout labor and delivery.</li> </ol>	<ol style="list-style-type: none"> <li>1. Needle breakage within sacral canal (use of the special malleable needle of stainless steel, discarding it after each five cases).</li> <li>2. Cannot be used in disoriented or uncoöperative patients, as the eclamptic and patients with toxic and functional psychoses, because of uncontrolled movement.</li> <li>3. Needle occasionally slips out during course of labor.</li> </ol>
Ureteral catheter technic, as described by Adams, Lundy, and Seldon [J. A. M. A. 122:152 (May 15) 1943] and Manalan [J. Indiana M. A. 35:564 (Oct.) 1942], and modified by Irving, Lippincott, and Meyer, and Siever and Mousel.	<ol style="list-style-type: none"> <li>1. Possibility of intrathecal injection almost nil.</li> <li>2. May be inserted before labor, when patient is not excited or in pain.</li> <li>3. Definitely is method of choice in eclamptic and disoriented patients.</li> <li>4. For cesarean section may be inserted safely into peridural space for 6 to 8 cm. with more prompt and high analgesia.</li> <li>5. Allows greater freedom of movement for patient in labor, with diminished possibility of catheter slipping out or producing trauma after large 13-gauge needle has been withdrawn.</li> </ol>	<ol style="list-style-type: none"> <li>1. Greater skill required for insertion of large needle and catheter.</li> <li>2. Greater incidence of peridural hematoma because of large needle.</li> <li>3. Large portal for potential infection opened with 13-gauge needle.</li> <li>4. More serious consequences from penetration of bone marrow of sacral corpora, rectum, and even cranial vault of baby in hands of untrained.</li> <li>5. Large port of entry may serve as source of leakage of solution through backflow.</li> <li>6. Unilateral analgesia more common, owing to deviation of catheter.</li> </ol>
Continuous (gravity) drip technic, as developed independently by Block and Rotstein [J. A. M. A. 122:582 (June 26) 1943] and by Postner and Buch [Am. J. Surg. 60:396 (June) 1943].	<ol style="list-style-type: none"> <li>1. Episacral insertion of needle more easily recognized, since pressure with hand over dorsum of sacrum stops the flow of the gravity drip.</li> <li>2. Apparatus simplified.</li> <li>3. Necessity for repeated handling of apparatus reduced, thereby reducing possibility of infection.</li> </ol>	<ol style="list-style-type: none"> <li>1. Less accurate control of analgesia.</li> <li>2. Necessity of constant attendance by nurse or doctor to watch level of analgesia.</li> <li>3. Amount of drug used during labor and delivery more, since much will leak out lower sacral and lower lumbar intervertebral foramina.</li> <li>4. Possibility of needle breakage or dislodging increased with patient constantly on back.</li> <li>5. Hazard of infection increased with patient on back to offset advantage of less handling of apparatus.</li> </ol>

separates will usually expel it within two to five minutes after delivery. When oxytocic drugs are given immediately after the birth of the baby, the incidence of trapped placentas is increased.

6. Continuous caudal analgesia should be started only after labor is definitely

established and the patient is in need of relief from pain.

The authors append a table of advantages and disadvantages of all the technics currently advocated.

In a recent personal communication the authors state that since January 6,



## QUESTIONNAIRE :

	N. A. Clinics	Authors' Series
A. Number of cases with continuous caudal analgesia.....	12,000	1,350
B. Number of cases with complete relief of pain.....	9,400	1,010
C. Number of cases with partial relief of pain.....	1,600	180
D. Number of cases considered as failures.....	1,000	160
E. Complications to the mother :		
1. Immediate reactions following injection.....	241	10
2. Number of cases with fall in blood pressure exceeding 20 mg. mercury in systolic reading.....	900	60
3. Increased nausea sometimes associated with vomiting.....	720	65
4. Infection at side of injection :		
(a) Simple cellulitis around site of injection.....	84	5
(b) Severe cellulitis or peridural abscess.....	6	1
5. Broken needles .....	32	9
6. Postdelivery headache .....	40	3
7. Neurologic sequelae attributed to method (these include urinary retention with need for catheterization more than once postpartum, residual backache, or hypesthesia) .....	300	6
F. Complications to the fetus (fetal distress and resuscitation problems) ....	74	5
G. Maternal mortality attributed to continuous caudal analgesia.....	3	1
H. Uncorrected fetal mortality.....	170	20
I. Fetal deaths presumed to be due to continuous caudal analgesia.....	3	1
J. Average interval between induction of analgesia and delivery. There were many answers to this question varying from 3½ to 8 hours.		
K. Observation regarding blood loss: Sixty-four of the 72 doctors reporting indicated that the blood loss was less with continuous caudal analgesia than with other methods.		

1942, they have the records of 12,000 mothers who received continuous caudal analgesia. These cases have been managed in 42 medical schools and teaching obstetrical hospitals throughout this country and Canada, where the authors have visited on invitation for the purpose of demonstrating this technic.

A questionnaire has been subsequently compiled and sent to all of these institutions in order to obtain some form of clinical evaluation of this method in obstetrics.

The percentage of success with this method seemed to vary directly with the experience of the operator, and the percentage of complications and failures seemed to vary inversely with the experience of the operator. For example, in the clinic of Majors H. H. Seiver and Lloyd Mousel at Fort Sam Houston, Texas, in 1000 cases there has been satisfactory analgesia produced in both labor and delivery in 96 per cent of the cases. In the authors' series of 1350 cases, 1190 cases or 89 per cent have

been managed through labor and delivery without resorting to any other form of analgesia or anesthesia.

**Ureteral Catheter Method**—A consideration of the technic, various uses, and some possible dangers of continuous caudal anesthesia is reviewed by Adams, Lundy and Seldon.<sup>14</sup>

After a preliminary trial of the method of Hingson and Edwards, the authors devised an alternative technic. This involved the use of a ureteral catheter inserted into the caudal canal through a large caliber needle and through which the local anesthetic solution was injected. This apparatus was developed with the idea of preventing possible breakage of and trauma from a semi-rigid needle in the caudal canal and to help permit greater freedom of movement of the obstetric patient during the course of her labor without the hazards of trauma or breakage of the needle.

Although the use of the catheter obviates the danger of breakage of the nee-

dle, other possible complications peculiar to its use must be borne in mind.

**Trauma** — The 13 gauge needle through which the catheter is introduced is large and can produce trauma if two or more attempts are made to insert it. If only one insertion is necessary, the trauma can be kept minimal as the needle need not be inserted into the caudal

On this basis the authors do not feel that multiple punctures should be made if the first one is unsuccessful.

If the catheter has been advanced too far into the caudal canal and it becomes necessary to withdraw it to the proper level, the 13 gauge needle should be withdrawn as well and both the needle and the catheter reinserted. If an at-

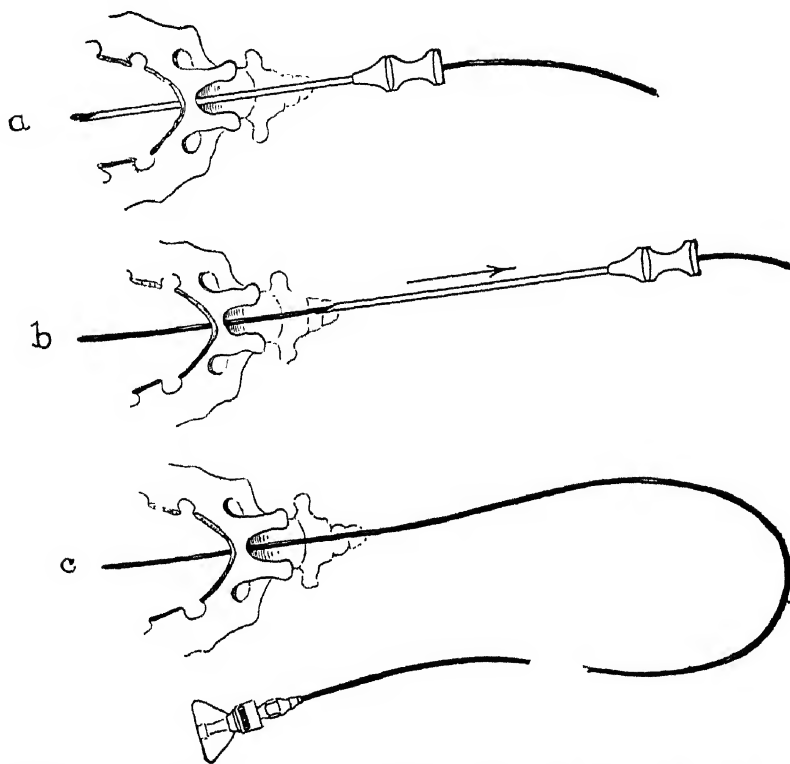


Fig. 3.—Diagrammatic representation of the relationship of the 13-gauge needle and that of the catheter to the caudal canal: *a*, Needle in place; catheter inserted through needle so that point of catheter is flush with the point of needle; *b*, catheter held in place and needle being withdrawn; *c*, catheter in place; needle has been removed. (C. R. Adams, J. S. Lundy, and T. H. Seldon: J. A. M. A.)

canal for a distance of more than one or two inches and it remains in the canal only for a matter of seconds or minutes.

If more than one puncture is required, trauma may occur. This will increase the possibility of irritation and infection. If a second puncture in a different location has been made, leakage of the local anesthetic solution through the original site of puncture has occurred. This lessens the chances of complete anesthesia and increases the possibility of infection.

tempt is made to withdraw the catheter without withdrawing the needle, the catheter may become caught on the sharp bevel of the needle. Traction on the catheter under such circumstances may result in shearing off its tip in the caudal canal.

Since most of the dangers, drawbacks, and untoward effects have been associated with certain technical difficulties which could not be foreseen in the early phases of the work by even experienced

physicians, it is suggested that for the present, at least, the use of the method be confined to institutional practice by persons trained and experienced in caudal anesthesia.

### Complications and Their Management

Some complications of caudal anesthesia and their management are pointed out by Gready.<sup>15</sup>

**Subdural Injection**—According to the routine advocated by Hingson and Edwards, and Gready and Hesseltine, a test dose of 8 cc. of a 1.5 per cent solution of *metycaine hydrochloride* (120 mg.) should first be injected and ten minutes allowed to elapse. The importance of this simple precaution cannot be too strongly emphasized.

The best treatment for this unwelcome accident is prevention, and the test dose, the author believes, is the best method available to avoid a massive subdural injection. It is further recommended that a test dose of 5 to 8 cc. be repeated ten minutes prior to each subsequent injection. This is especially important when the needle technic is used, since the needle may pierce the dura at any time during the procedure.

The spinal cord normally ends at the level of the first lumbar vertebra, with the dural sac containing spinal fluid and the cauda equina tapering to a point in the sacral canal at the level of the second sacral vertebra.

The important fact that the dural sac may extend lower than the second sacral vertebra should be kept constantly in mind. If the patient is thin and the sacrum short, the use of a 2½-inch rather than a 3-inch needle lessens the danger of perforating the dura.

Should massive spinal anesthesia occur, treatment should be instituted immediately. The patient should be sup-

ported in a sitting position, and a *lumbar puncture* should be done using a large needle so that the fluid will flow rapidly.

Approximately 100 cc. of spinal fluid may be withdrawn. The flow can be hastened by compression of the jugular veins in the neck. Forced drainage may also be accomplished by giving *0.45 per cent saline solution* intravenously while the lumbar puncture needle is in place. Even though the respiratory center is anesthetized, the method should still be tried in order to prevent involvement of the vasomotor center, which is at a higher level.

**Infection**—Infection ranks second in importance to massive spinal anesthesia. It may occur either in the tissue outside the sacral canal or in the epidural space. The latter is more serious because of its proximity to the cord and nerves of the spinal and sacral canal.

The principal etiologic factor in this type of case is obviously faulty technic. The site for injection should be as thoroughly cleaned and prepared as for a major surgical procedure. If the needle technic is used, the only bacteriologic weak point in the equipment once the tubing is connected is the plunger of the syringe.

**Intravenous Injection**—Preliminary aspiration must always be carried out to minimize this danger. If blood is obtained the position of the needle must be changed until blood can no longer be aspirated and then the injection should proceed slowly and expectantly.

It is imperative that respiration be maintained, by artificial means if necessary. One of the quick acting barbiturates, such as *evipal sodium* or *pentothal sodium*, should relieve the convulsions immediately.

**Idiosyncrasy**—Every patient should be questioned prior to the initial injec-

tion as to a history of allergy and especially as to previous reactions to these drugs. If a reaction occurs the immediate hypodermic administration of *epinephrine hydrochloride* is recommended. Convulsions, should they occur, are controlled by using *barbiturates* intravenously, care being taken not to give an overdose.

**Injury of Nerve Roots**—This occurs very infrequently.

**Breaking of the Needle**—The incidence of this complication has been considerably reduced since the development of the malleable needle and catheter technic. The danger can be still further minimized by keeping the patient on her side during labor and then giving an injection and removing the needle just before she is placed on her back for delivery.

**Changes in Blood Pressure**—Of 39 patients with an anesthetic level at or above the umbilicus, 26 showed drops of more than 20 mm. Two patients definitely had shock reactions, the systolic pressure dropping to zero from 158/110 and 90/60, respectively. Every one of these patients responded to *ephedrine sulfate* administered hypodermically and *oxygen inhalations*.

### Caudal Anesthesia for Cesarean Section

The single injection technic of caudal anesthesia for cesarean sections is reported by Lahmann and Mietus.<sup>16</sup>

This series is comprised of 46 laparotomies and two Porro cesareans. In no instance was a classical section performed. Three of the women were subjected to a Madlener sterilization.

The only postoperative complication worthy of note was a pelvic abscess which developed in a primipara subjected to a low cervical section after a protracted labor.

The anesthetic agent used for the series was a 2 per cent solution of *metycaine*. There was some variation in the volumes injected. In two of the patients, 40 cc. were injected; in four cases, 45 cc. were used; in two instances, 50 cc. were administered, and in the remaining 40, 60 cc. of the metycaine were given.

All of the patients received a barbiturate preoperatively. Four of the series were given 0.194 Gm. (3 gr.) of *sodium amytal*, while seven received 0.194 Gm. (3 gr.) of *pentobarbital*, and the remaining received 0.289 Gm. (4½ gr.) or more of pentobarbital. All but nine were given a preoperative hypodermic injection of *atropine sulfate*, 0.0004 Gm. (¼<sub>50</sub> gr.).

In three of the 48 cases, the block failed completely. In two instances the caudal block wore off before the operation was completed. Here, closure of the abdomen was affected under intravenous *sodium pentothal*.

Untoward effects were occasionally witnessed. A sudden transitory fall in blood pressure was seen not infrequently, particularly in those instances where larger volumes of the anesthetic agent were instilled.

Invaluable for operative obstetrics and particularly suited for cesarean sections, the authors feel that caudal block, not at all unlike spinal and inhalation anesthesia, defies promiscuous use and demands a certain degree of consideration and respect.

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## LABOR

### Vaginal Antisepsis

Mayes<sup>17</sup> reports 11,000 vaginal deliveries without a death from puerperal infection at the Methodist Hospital, Brooklyn. During the last 18 years the patients in the obstetrical department of the Methodist Hospital have been pro-

tected from puerperal infection by the vaginal instillations of a 4 per cent solution of *mercurochrome* during labor and at the time of delivery.

The adequacy of this protection is shown by the fact that there have been 25,347 vaginal deliveries since January 1, 1928, with only two deaths from puerperal sepsis. There has been but one such death in the last 20,048 cases and not one in the last 11,000 vaginal deliveries.

The present report covers the period from January 1, 1934, to January 1, 1942, a record of 13,763 patients with a morbidity of 7.8 per cent previously unreported. If we omit the cesarean sections the morbidity is 5.3 per cent and the corrected morbidity is 3.3 per cent.

There were 528 cesarean sections, with a morbidity of 54.9 per cent and 12 deaths, one of which was from infection.

Among the vaginal deliveries there were 6247 operative deliveries with no septic deaths.

Thirty-two per cent of all the patients delivered during the last eight years were examined vaginally, and 31.8 per cent of the patients with a morbidity during the same period had vaginal examinations. The morbidity for the patients examined vaginally was 8.3 per cent.

During 1940 a 1 to 1000 solution of *zephirin* was used on 837 ward patients, with a morbidity of 8.7 per cent.

The authors conclude that since no harmful effects have been found or reported following the use of vaginal antiseptics, it would seem that a procedure so simple, so sound in principle, should be a routine recommended by all.

### Cervical Dystocia

The effect of local anesthesia by means of *pudendal nerve block* with novocain on cervical dystocia occurring late in the first stage of labor is reported by Bunim.<sup>18</sup>

The procedure is described as follows: The index and middle fingers of one hand are inserted in the vagina and the ischial spine is located and used as an anatomic landmark. A No. 19 needle attached to a 20 cc. syringe is inserted medially, half way between the rectum and tuberosity of the ischium. When the needle is felt by the vaginal fingers it is directed downward and laterally to a point just below the ischial spine. This directs the needle into Alcock's canal. Then 20 cc. of 1 per cent *novocain* is injected at this point. One must always remember to pull back the plunger before injecting the solution, for, as pointed out above, the pudendal nerve is accompanied by the internal pudic vessels in its course through Alcock's canal.

The needle is left *in situ* and the syringe is disconnected, refilled with 15 cc. of the solution of 1 per cent novocain, and reattached to the needle. The latter is withdrawn slightly and directed against the ischial tuberosity, where the anesthetic is injected around the lateral cutaneous femoral nerve. Then 15 cc. of 1 per cent novocain are injected superficially in an oblique and radial manner from the original site of insertion of the needle, to the inner aspect of the labium majus, thus paralyzing the terminal branches of the ilioinguinal nerve. A similar procedure is carried out on the opposite side. Thus, a total of 100 cc. of novocain is used for both sides. As seen from the above, the needle has to be inserted only in two places, one on the right and one on the left side, without the need for removing it entirely during each procedure.

The author recommends this procedure for any case in which rapid dilatation of a rigid cervical rim is desired.

Thirty-eight patients were treated for cervical dystocia late in the first stage of labor by the technic described above.

Thirty-one of the patients were primiparas and seven were multiparas. There were no maternal deaths among the 38 cases.

There was one stillbirth, due to intracranial injury following the application of forceps, in a case of cephalopelvic disproportion.

### Occipitoposterior Position

The treatment of occipitoposterior position is discussed by Hennessy.<sup>19</sup>

In his opinion it is much better for labor to be definitely established and sedation not given until dilatation of the cervix reaches 3 to 3.5 cm. If sedation is given too early, it tends to slow and

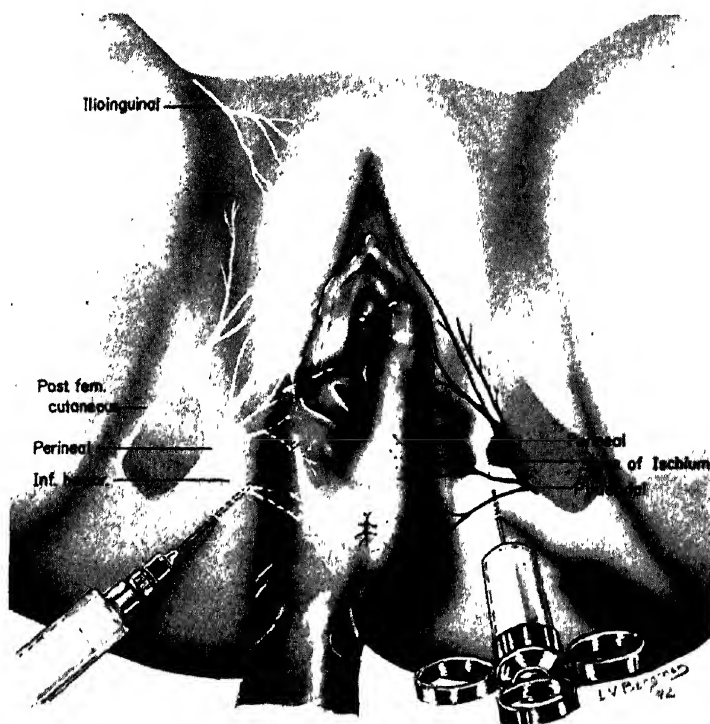


Fig. 4—Diagram showing the procedure used for blocking the nerve supply to the pelvic floor. (L. A. Bunim: Am. J. Obst. and Gynec.)

Generally about five to ten minutes after the anesthetic is injected, a relaxation of the perineum is noticed. In another ten minutes the spasticity of the cervix disappears and dilatations progress satisfactorily if the uterine contractions continue. If there is uterine inertia, small repeated doses of *pituitary extract*, 0.12 cc. (2 minims), will initiate further progress.

This procedure failed in only one case. The average duration of labor for the 38 cases was 31.9 hours, and the average arrest of progress lasted 6.3 hours.

prolong labor and additional sedation is required, leading in some cases to increased morbidity and birth injuries. While the cervix is dilating, a Beck binder is applied. The bag of waters is preserved as long as possible, both for its dilating factor and to facilitate version if this is indicated. If dilatation is unduly slow, the anterior end of the fetal head may be forced upward, thereby increasing flexion. No intervention is made until the cervix is completely dilated and effaced; then, if the head remains unengaged, podalic version is performed.

This is more easily done before the membranes have ruptured; therefore, when all conditions have been fulfilled, it is better to deliver early. If the membranes have already ruptured and the head is still high when the os is fully dilated, version should be done as promptly as possible before the amniotic fluid has drained away and while there is still a sufficient amount of liquor remaining in the sac.

When an engaged head is at the spines, from  $1\frac{1}{2}$  to 2 hours of labor is allowed for rotation; if it is below the spines, about an hour is allowed. Occasionally this rule is broken to permit better molding in the case of a fairly large head, provided mother and child are in good condition. Manual rotation properly performed is simple and causes less trauma than other methods. The author uses Schumann's modification of the Pomeroy technic as follows: The hand whose palmar surface will slip over the occiput is introduced into the vagina; the first and second fingers slip past the head and seek the anterior axilla, the head lying loosely in the palm of the hand. With the other hand making abdominal pressure, the shoulder of the child is firmly pushed around the anterior aspect of the pelvis until the body has been rotated almost 180 degrees. The occiput becomes dislodged from under the promontory of the sacrum and turns with the body into an anterior position. When this is accomplished, the hand is not withdrawn until after one blade of the forceps has been applied to the head, acting as a wedge to prevent the occiput from rotating again to the posterior position. The second blade is then applied, and delivery follows.

In forceps rotation, Hennessy prefers the modified Scanzoni method as described and advocated by Bill. He tries to rotate the head in the station in which

it lies, just as would be done with the hand, although with the forceps there is apparently less displacement of the head. If this is properly done there should be no laceration or injury of the child. This procedure has been followed in several hundred cases and in only two instances (both the babies were large with large heads) was it impossible to rotate the head by forceps. Only nine cases in the series were delivered by Kielland's forceps, since he has not found this instrument successful when used as described by Kielland.

### Breech Delivery

The intrinsic risk of uncomplicated breech delivery is discussed by Tompkins.<sup>20</sup>

The author selected every case personally delivered by the 17 obstetricians at the Lying-In Hospital in Philadelphia after their certification by the American Board of Obstetrics and Gynecology.

Two hundred and eleven cases of breech presentation are the basis of this study. One hundred and eighty babies were delivered vaginally. Thirty-one patients, 14 per cent, all with single pregnancies, were delivered by cesarean section.

There was a total of 146 uncomplicated breech deliveries weighing over 1500 Gm.; in these, four babies died. The fetal mortality rate of 2.7 per cent for this group represents, as nearly as can be determined, the intrinsic risk of breech delivery in this hospital. Two of these four deaths could have been prevented, and, in retrospect, should have been prevented by cesarean section.

In the management of breech presentation the following policies are recommended:

1. An x-ray study of the maternal pelvis should be made in nulliparous patients.



2. The membranes should seldom be ruptured artificially because of the danger of prolapse of the cord and the increased risk if cesarean section is subsequently necessary.

3. The patient should be fully anesthetized before delivery.

4. Decomposition of the breech is to be undertaken only in exceptional cases.

5. Traction is not to be used until the breech has passed the introitus.

6. In primiparas a generous episiotomy is advisable.

7. After delivery of the umbilicus the back should be turned uppermost to prevent posterior rotation of the occiput, and constant pressure should be maintained on the fetal head from above to prevent extension.

8. Forceps, preferably Piper's after-coming head forceps, should be utilized in all but the easiest cases.

9. Since there is no certain means of determining disproportion, consultation should be sought early in every doubtful case.

### Hypnosis in Labor

The use of the hypnoidal state as an amnesic, analgesic, and anesthetic agent in obstetrics is reported in 11 patients by Korger and DeLee.<sup>21</sup>

There was only one failure in this small series of cases.

**Management of the Prenatal Period**—The patient is placed in a deep hypnotic state before the seventh month of gestation. Posthypnotic suggestions are given to the effect that her labor will be entirely painless, that she will have no recollection of the entire procedure, and that she will look forward to her confinement with a feeling of joy and happiness instead of dread and anticipation. Posthypnotic suggestions last about a month, and when repeated often enough the effect will become permanent. The

gravidia is then conditioned to the voice of the operator. Suggestions are given that she will fall into a deep hypnotic sleep at a given command. In addition, she is told she will follow all suggestions given her during this period.

The patient returns every two weeks and the same suggestions are repeated to her in the hypnotic trance, which is a state of increased hypersuggestibility. After the proper training or conditioning the gravida can be put into an amnesic, analgesic, and anesthetic state in five or ten seconds.

**Management During Labor and Delivery**—Hypnotic sleep is induced when the gravida is in active labor, or when the cervix is dilated between 2 to 4 cm. The patient is told that her sleep will be deep and continuous. Also, she will hear only the commands of the operator.

These patients, after careful preparation, will be most cooperative during labor. They can converse with the operator, and ask for food, urinate, or defecate at their own request. They lie motionless and require no particular attention except routine care. The normal mechanism of labor is not interfered with and during the latter part of the second stage the gravida can be told to bear down with each contraction, thereby facilitating the completion of the expulsive stage.

The respiration is diaphragmatic in type, the pupils are usually fixed and dilated. The limbs can be made cataplectic or flaccid during delivery and complete relaxation of the entire body can be produced simply by command. Any type of operative delivery is facilitated. Speed is not essential, since the gravida will sleep until told to awaken. Posthypnotic suggestions are then given that she will be sound in mind and body, and will have no after-effect such as headache or

pain. All patients wake up promptly when told to do so.

There are no untoward effects on the mother or baby.

### Cesarean Section

**Evaluation of Types of Section and Their Indications**—The corporeal or low fundal section is indicated in all elective cases, including operations done for placenta previa and abruptio placentae. This is because the method is the simplest, quickest, and lends itself most readily to infiltration analgesia. It is just as safe under these circumstances as any other procedure.

The low cervical section is indicated in women who have undergone a test of labor, in whom the lower uterine segment is well distended by the presenting part, and who may or may not be potentially infected.

Neither of these operations is wise when definite infection is present, since neither protects the peritoneal cavity against spill. Under such circumstances vaginal delivery by whatever means is available, truly extraperitoneal section, exteriorization, or hysterectomy, is the only justifiable procedures.

The operation advocated by Schumann<sup>22</sup> is a purely elective procedure, done before the onset of labor or very early in the first stage, the indications being generally cephalopelvic disproportion, toxemia, placenta previa, or systemic disease of the mother.

**Morphine sulfate**, 0.013 Gm. ( $\frac{1}{8}$  gr.), and **scopolamine hydrobromide**, 0.0004 Gm. ( $\frac{1}{150}$  gr.), are administered hypodermically. Thirty minutes after the hypodermic the woman, her eyes lightly covered, is wheeled into the operating room where all is in readiness. Operation is begun under local anesthesia, using  $\frac{1}{2}$  per cent *novocain*.

A midline incision from the umbilicus downward about 14 cm. is then made, the peritoneum infiltrated and incised. A No. 2 chromic catgut suture is then introduced at the upper angle of the incision, passing through fascia, muscle, and peritoneum, then passing into the uterine muscle and out on the opposite side. This suture is tightly tied, the ends held by a hemostat. A similar suture is placed at the lower angle of the incision just at the point of attachment of the vesical fold of the peritoneum. By this means the uterus is anchored to the abdominal incision, and the abdominal walls closely approximate the sides of the uterus. Intestines and omentum are not seen and there is little or no spill of blood and amniotic fluid. Packing is not used. A semilunar incision through the uterine serosa is then made, beginning and ending at the upper and lower sutures and with its convexity toward the operator. A peritoneal flap is very easily turned back by grasping the middle of the incision with an Allis forceps and with a few snips of scissors or simply blunt dissection the flap is turned back until the uterine muscle immediately underlying it is exposed. The uterine wall is then carefully incised for a distance of 2 or 3 cm., until a pouch of membrane bulges through the opening. A gauze pad is laid about the bulging membrane and with trocar and suction apparatus the liquor amnii is drained away. The field being dry, the uterine incision is lengthened, usually from the upper to the lower suture, either by cutting with scissors or, as is preferable, by tearing the fibers apart with the fingers. It is remarkable, states Schumann, to note the approximation of the uterine walls upon the completion of the operation when the uterus has been opened by tearing the fibers. This is because the uterine muscle fibers are not severed but merely

displaced and pulled apart and tend to readjust themselves as soon as uterine contractions begin. One cubic centimeter of *pituitrin* is given at the beginning of the uterine incision and the baby is withdrawn by breech extraction. Hemorrhage from the uterine wall is ordinarily

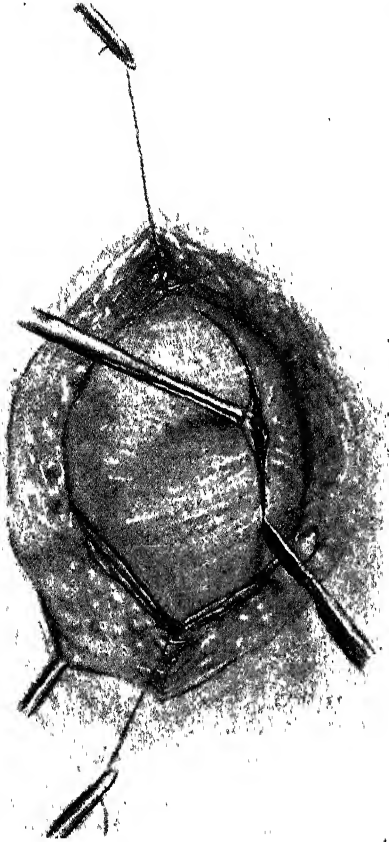


Fig. 5—The uterus has been sutured to the abdominal wall and the formation of the peritoneal flap is begun. (E. A. Schumann: Am. J. Surg.)

negligible but if sinuses bleed freely they may be clamped with T hemostats covered with rubber tubing. The usual time for the separation of the placenta is permitted and this organ generally bulges up into the uterine wound in from five to ten minutes after the extraction of the baby. Should this not be the case, the placenta may be separated in the ordinary manner.

The empty uterus is then closed by two layers of interrupted or continuous



Fig. 6—The peritoneal flap being developed. (E. A. Schumann: Am. J. Surg.)

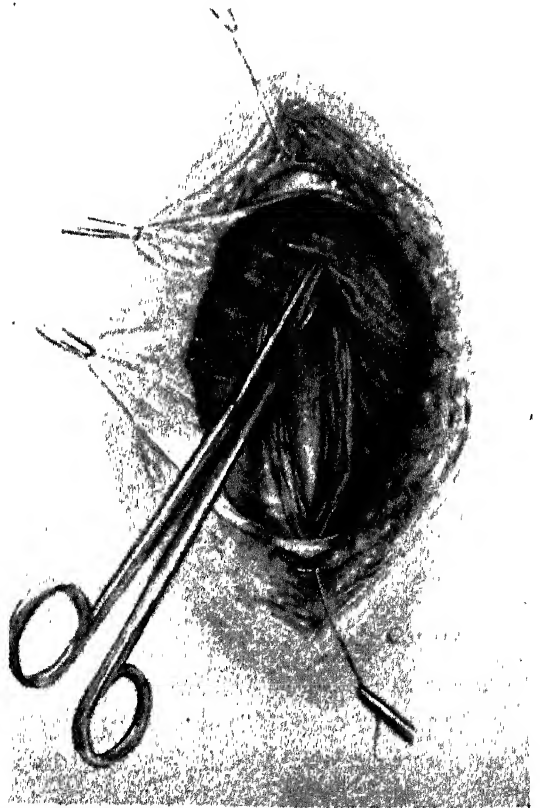


Fig. 7—The underlying uterine wall is being incised. (E. A. Schumann: Am. J. Surg.)

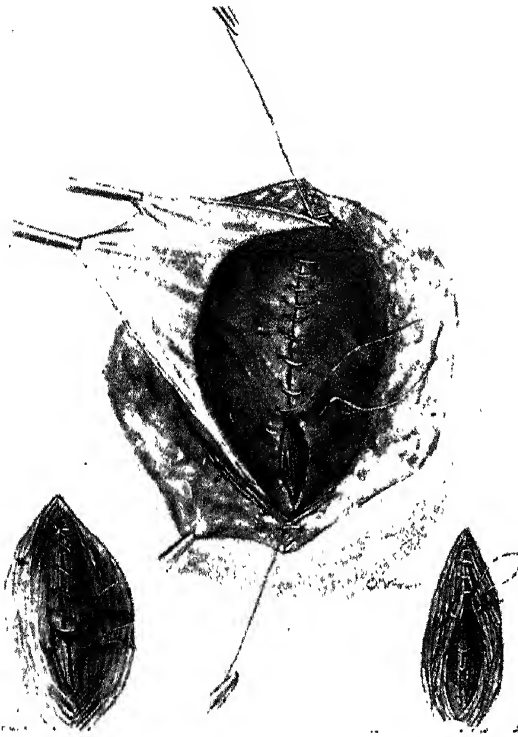


Fig. 8—The uterine muscle is closed.  
(E. A. Schumann: *Am. J. Surg.*)

catgut sutures, depending upon the predilection of the surgeon, and finally the peritoneal flap, which now extends far beyond its original area, is utilized to cover the suture line in the uterus, being attached by a continuous suture of No. 00 catgut. In order to close the abdomen without permitting intestines or omentum to protrude into the wound, the lower suture attaching the uterus to the abdominal wall is cut first and the parietal peritoneum closed by a continuous suture until the upper attachment is reached. This is then cut and the closure of the peritoneum and the rest of the abdominal wall completed. Should it be desired to sterilize the woman, the lower suture is cut, the uterus gently rotated upon the upper suture until the tube appears, and when this structure has been anesthetized by further infiltration, any desired procedure for sterilization may easily be completed.

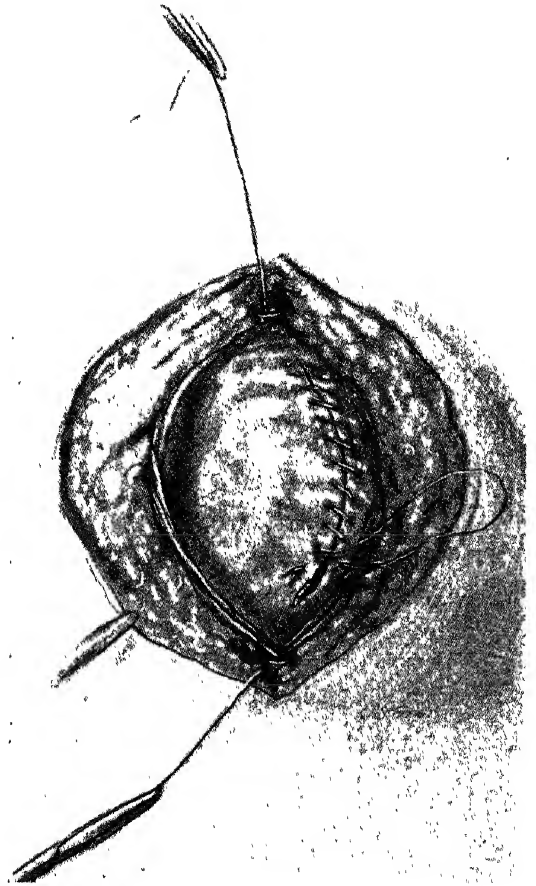


Fig. 9—The peritoneal flap completely covers the uterine incision and is being sutured in place. (E. A. Schumann: *Am. J. Surg.*)

### Postoperative Therapy

**Intravenous Therapy**—Of interest to the obstetrician contemplating a surgical procedure is a panel discussion on intravenous therapy by Russel L. Haden, Jonathan E. Rhoads, Max Strumia, Lester Hollander, and George J. Thomas.<sup>23</sup>

For routine administration after operative procedures, about 3500 cc. of fluid intake is advisable during the first 24 hours; following that, about 2500 cc. for each subsequent 24 hours, until the patient is able to take fluids by mouth.

Years ago nearly all of this was given as physiologic saline solution, that is, 0.85 per cent salt in water. A number of ill patients were unable to dispose of this amount of salt, which would amount

to over 30 Gm. a day at times, and an extensive edema resulted. The protein deficit which many of these patients had undergone for a period of days frequently resulted in low serum proteins and this also exaggerated the tendency to edema. Usually, replace only the urine with **salt solution**, for which it is estimated 1000 cc. will suffice. The remainder of the total fluid intake is generally given as **5 per cent glucose** in water.

Give no intravenous medication in the sense of replacement therapy until the chlorides, the hemoglobin concentration, and the total plasma proteins have been determined. The replacement therapy is judged according to findings.

When water is given routinely in the form of 10 per cent glucose solution, if that solution is administered too rapidly, glucose passes into the urine, where it is found almost regularly in patients getting either 10 per cent glucose at the regular rate—say, 10 cc. per minute—or in patients receiving 5 per cent glucose, but receiving it at an exaggeratedly rapid rate.

Since water is generally the element that one has in mind, the ideal method is to give it in isotonic form, that is, either with saline or 5 per cent glucose.

There is a group of patients in whom edema will develop from isotonic salt solution, even if it is given within what we would consider the normal intake. Such patients have a hypoproteinemia to start with, to a critical level where peripheral edema is not noticeable. This type of patient; of course, is very common in surgical practice.

**Plasma** is not a blood substitute. It is better indicated as a blood derivative. Nothing substitutes for whole blood.

In the administration of plasma, there are two general ideas or lines of thought. One is that it be used when clinically preferable to whole blood or other intra-

venous therapy. The second consideration is that it lends itself to preservation, transportation, and rapid use when other fluids would be difficult to use.

**Contraindication to Plasma**—1. If a patient has a severe hemorrhage, which is continuing at the time of treatment, plasma cannot be used because it would simply dilute the blood until a point is reached where the total oxygen-carrying capacity is so low that anoxia results and the purpose of intravenous therapy is defeated. Where there is tissue anoxia, there is continued permeability and the condition that maintains the cause of shock—loss of fluid—will go on unchecked.

2. Second, if a patient has carbon monoxide poisoning or any form of poisoning in which there is disability of the oxygen-carrying capacity, this blood must again be used.

3. Third, in a case of purpura, where the blood-clotting mechanism replacement is to be depended on, use fresh whole blood.

Burns, late shock, severe hypoproteinemia from liver disease, and severe forms of nephrosis are clear indications for the use of plasma in place of whole blood. In patients with ordinary shock, use whatever is available in the shortest period of time. That is why plasma usually has the advantage over whole blood.

**Preservation of Plasma**—Strumia has kept plasma in the frozen state for a period up to two and a half years without any change in the constituents or in the therapeutic effect. He considers it a very dangerous procedure to keep plasma in any state that does not prevent bacterial growth and progressive degeneration of the plasma proteins.

Most of the reactions that have been reported are not due to the plasma itself, but to its improper preservation. There are only two ways to avoid that danger.

One is to freeze the material by a rather simple and economical procedure. The other one is to dry it, which is a much more expensive procedure in the laboratory.

If the sterility of the material is beyond question, there is no doubt that at room temperature plasma can be kept for a period of a month, two months, or maybe a little longer. After that flocculation begins.

One of the worst methods of keeping plasma is in the refrigerator. In 36 hours at 4° C. there is an irreversible precipitation of certain proteins, which means that the plasma must be carefully filtered before administration. Preservation of plasma at 2° and 4° C. slows up bacterial growth but does not prevent it. Therefore, preservation of plasma at 2° C. does not have any advantage. If plasma which has been preserved in the liquid state must be used by all means keep it at room temperature.

**Intravenous Analgesics**—Frequently, physicians find it necessary to administer some agent to relieve a renal or biliary colic or some other colic in patients. The physician gives a large dose of *morphine* subcutaneously or intramuscularly and sits at the patient's bedside, hoping that the effect of the morphine will soon take hold and the patient will get relief. Some individuals with this type of colic will receive immediate relief, within 15 or 30 seconds, if the morphine is given intravenously, slowly, and making sure that it is barbotaged as it is being given.

The dose generally given is one-third of what is usually given hypodermically.

In anesthetic convulsion cases a barbiturate intravenously gives relief within a few seconds of time, and it is much safer. Thomas prefers *pentothal sodium*. It is quickly eliminated from the body and the anoxia will not last as

long. One should make sure the patients have a good tidal volume as far as breathing is concerned and should not allow anoxia to occur.

### Coma and Shock

Taylor<sup>24</sup> states, in a panel discussion on shock, in obstetrics patients may go into shock and there are those in whom hemorrhage develops. Dr. Moon is committed to the elimination of the term "hemorrhagic shock." One of the important points that he brought out is applicable to the patient in obstetric shock (which is the same as traumatic shock). The smallest amount of hemorrhage may prove fatal. Such a patient, it has been experimentally and clinically shown, cannot absorb or retain any fluids, whether they are crystalloid, colloid, plasma, or what not. Not only the degree of hemorrhage but the time factor must be taken into consideration.

All obstetric patients should have their hemoglobin and red blood cell count estimated on admission to the hospital, at least prior to delivery. Then there is something to work on if anything goes wrong during delivery or shortly after, such as rupture or inversion of the uterus. In inversion of the uterus, one of the classical symptoms is shock out of all proportion to the amount of hemorrhage.

One of the important signs from the diagnostic standpoint, in addition to the hematocrit reading, the red blood cell estimation, the hemoglobin, and the specific gravity of the blood, is the countenance of the patient, the hippocratic facies that is apparent in all patients in shock. They have the same drawn expression, cyanotic fingertips, and beads of perspiration as patients in shock from peritonitis.

In obstetrics, many patients fear delivery because they have been led to believe so much. The patient who has been

in labor a long time is exhausted, and, in addition to being fatigued and afraid, is dehydrated. Here is where intravenous glucose therapy is of great benefit in preventing obstetric shock.

In the line of treatment, with the *Trendelenburg position* and the use of *heat*, Taylor thinks the tendency is to keep the patient too warm. Excessive heat is detrimental just as is too much loss of blood.

The use of oxygen should be stressed in the treatment of obstetric patients in shock.

As to the use of drugs, such as *adrenalin* and *ephedrine*, they are useless. The arterioles are already constricted in the process of shock.

Pituitary products may cause shock; in pregnancy there is hyperactivity of the pituitary body, of course, and if *pituirin* is used, it should be used very discreetly.

## PUERPERIUM

Postnatal observation of pelvic tissue damage in 1000 patients is reported by Gainey.<sup>25</sup> The author emphasizes that three definite anatomic planes are of recognized importance.

1. The upper pelvic floor is made up of the parametrial fascia with its localized condensations forming the uterosacral, Mackenrodt's ligaments, and the much weaker cervicopubic fascia. Damage to this plane is manifested by cystocele, uterine descensus, and enterocele.

2. The pelvic diaphragm consists of the pubococcygeus, ileococcygeus, and coccygeus muscles with their envelope of endopelvic fascia. Damage to this plane was recorded by palpation of areas of detachment, or atrophy, of the first two, relaxation of the introitus after voluntary effort at closure, and detachment

of the urethra from its retropubic position.

3. The third plane, the urogenital trigone, closing the anterior triangle of the bony outlet with its fascial planes and musculature inclusions, is one of the areas most vulnerable to damage due to parturition. Damage of this plane was recorded by noting relaxation of the vestibule, detachment of urethra, and by comparing with normal the "anovaginal" portion as determined by digital rectal examination. In addition to these planes of tissue structure, other injury occurs which is of vital importance to the patient's welfare.

Review of the damage observed in the entire group reveals parturition as a destructive process. Three hundred and thirteen (31 per cent) of patients suffered damage with resultant atrophy or detachment to the levators ani, varying from partial to complete damage of one or more components, the pubococcygeus being most vulnerable. One hundred and seventy-eight (18 per cent) manifested detachment of the urethra from its normal retropubic position, indicating damage to that portion both of pelvic diaphragm and urogenital trigone. Three hundred and eighty-nine (39 per cent) had gaping of introitus when relaxed, and of these, 143 (14 per cent) remained gaping when voluntary effort at closure by levators was observed. Two hundred and thirty-five (24 per cent) showed what was arbitrarily set as less than 60 per cent of normal height or thickness of the anovaginal portion of the urogenital trigone.

*Episiotomy* offers greatest protection to this area as noted when the two groups of primiparas with episiotomy and those delivered without apparent laceration are compared.

Two hundred and thirty-six (24 per cent) of the patients showed detachment



of the vaginal wall from the endopelvic fascia on either side of the rectum and actual rectocele recorded in 120, or 12 per cent. Diffuse detachment or prolapse was noted in 202, or 20 per cent. Obliteration of the anterior fornix was partial to complete in 311, or 31 per cent. Cystocele was interpreted by definite saccular or diffuse bulging of anterior vaginal wall was present in 264 patients, saccular bulging being 11 per cent of total. Enterocoele was not observed.

Nine instances of uterine descensus were observed, and in only one was it complete, all being in multiparas.

In a discussion of this paper, T. Montgomery maintains that with the free use of median episiotomy, extended when necessary off to the side of the anus and the rectum, extensive urogenital trigone damage can be avoided. The main indication for episiotomy is to prevent pressure of the head against the bladder, the urethra, and the fascial structures of the urogenital diaphragm.

To accomplish this with episiotomy, Montgomery advises that certain principles be kept in mind: (1) Episiotomy must be performed early and before the head has greatly distended the lower birth canal; (2) episiotomy must be free; (3) the repair of this incision must be conducted with just as great care as a gynecoplastic operation, which means that the field must be cleared of blood, must be properly exposed, and the procedure done in an orderly anatomic fashion; (4) the use of fine grades of catgut, notably 00 chromic catgut. There is very little tension in this area and all that one needs is material of sufficient tensile strength to hold the tissues together.

Montgomery finds the greatest degree of damage of fascial structures and underlying muscle tissue in the slender primipara who has a rapid, almost pre-

cipitous labor. Here, as Dr. Gainey has pointed out, damage of the urogenital diaphragm occurs, submucous injuries of the pubococcygeal portion of the levator ani muscle, rupture of the true ligaments of the uterus, and a resulting early tendency to cystocele, rectocele, and descent of the puerperal uterus. While the slow, difficult labor of the less feminine type of patient may be more worrisome to the obstetrician, generally there is better recovery from tissue damage.

### Lactation

**Stimulation with Prolactin**—The lactogenic effect of prolactin in the human being was investigated by Winson.<sup>26</sup> Three groups of puerperal patients were studied as follows:

**Experiment 1**—In the first group of 40 puerperal women, 20 were given prolactin and 20 were used as controls. The 40 comprising the two groups, treated and untreated, were not permitted to nurse their infants because of prematurity, etc. Prolactin injections of 100 I. U. twice daily were started on the first postpartum day and continued for five consecutive days. Results show that the average quantity of milk secreted by the prolactin-treated mothers was more than twice the average quantity secreted by the untreated women.

**Experiment 2**—One hundred patients were given 100 I. U. of prolactin twice daily from the first to the fifth day postpartum, inclusive. The infants of the treated and control groups were breast-fed during the sixteen days of observation. The infants were nursed at intervals of four hours beginning 12 hours after birth. The infants whose mothers received prolactin lost less weight and regained weight faster than the infants of the control group. Three-fourths of the infants regained or exceeded their birth weight within the ten-day period

when prolactin was used, whereas only one-sixth of the control group regained their birth weight during that period.

**Experiment 3**—Prolactin, 100 I. U. twice daily for five days, was given to improve the yield of milk in a group of 50 lactating women when it was apparent, from five to seven days after birth, that the milk supply was markedly insufficient, as determined by the excessive weight loss of the infants maintained solely by breast feeding.

The results obtained were as follows: 36 of the 50 patients (72 per cent) showed a definitely good response. Of the remaining 14 patients, four (8 per cent) exhibited partial improvement and ten (20 per cent) showed response.

### Postpartum Psychosis

The use of progesterone in the treatment of postpartum psychosis is advocated by Schmidt.<sup>27</sup>

The constant precipitating factor and the favorable prognosis for recovery indicate that postpartum psychosis is a clinical entity and is due to some disturbance of a physiologic nature resulting from the sudden termination of pregnancy.

The recurrence of the psychosis associated with the menstrual cycle in the case reported by the author suggested that the condition had some relationship with the hormone balance. The most probable disturbance of the balance would likely be due to the sudden loss of a superabundance of progesterone furnished by the placenta.

The loss of a large amount of progesterone at delivery and the accepted relationship of estrogen to premenstrual tension indicate that the psychosis probably results from an excess of this estrogenic hormone in the circulation. Excellent results were obtained by the administration of this hormone, 10 mg. daily.

It is suggested that adequate dosage of progesterone be used in the treatment and that the menstrual cycle be re-established if necessary.

## NEWBORN

### Effect of Irradiation of Mother

Irradiation of the spleen and pituitary for control of puberal bleeding with birth of a normal child following treatment of the mother is reported by Kaplan.<sup>28</sup>

The author feels that the fear that irradiation may do harm to the generative organs is one of the main reasons why this well-tested method is not more generally utilized in the treatment of irregular bleedings in young girls.

Treatment over the spleen can be administered without much hazard of affecting the ovaries, the indirect effect on the ovaries being considerably less than the supposed damage resulting from direct ovarian irradiation in young women and girls. In menorrhagia at puberty or just beyond this period, roentgen therapy to the spleen and on the pituitary can be safely administered, states Kaplan, without interfering with subsequent ability to bear children.

A young girl of 15 suffering from irregular menstrual bleeding and hemorrhage, previously having been treated with medication without response, was moderately controlled by roentgen therapy to the spleen and pituitary, and eventually resumed normal menstruation. She married at 22½ years and gave birth to a perfectly normal child about two years later. Roentgen therapy, while controlling the uterine bleeding, had no injurious effect on the reproductive organs of the mother or on the child.

Hofbauer<sup>29</sup> cautions, however, that clinical observations of the occurrence of diabetes insipidus, if temporary, and of adiposogenital atrophy in the wake of

pituitary irradiation in young persons provides a warning note that this treatment should be used with discernment. In harmony with the experimentally established fact mentioned that the brain of the growing organism may be injured by the application of radiant energy, he feels that pituitary irradiation has no place in the treatment of gynecologic disorders in persons under 20 years of age irrespective of "the dosage and method properly selected."

### Rh Blood Factor

The importance of the Rh blood factor in erythroblastosis is described by Potter, Davidsohn, and Crunden.<sup>30</sup>

The Rh factor is an antigenic substance found in human blood cells. It is inherited as a Mendelian dominant. It occurs only in the red blood cells. When cells containing the Rh factor (Rh+) are introduced into the blood stream of a person in whom the factor is absent (Rh-), agglutinins against it may be developed (*i. e.*, it has iso-immunizing ability. If blood containing the Rh factor is introduced into an individual who is Rh negative, and antibodies are produced which are capable of agglutinating Rh positive cells, the introduction of Rh positive blood by subsequent transfusion into such a sensitized person may result in the agglutination of the donor's cells in the recipient's blood stream even though both individuals are of identical major blood groups.

If a fetus inherits the Rh factor from an Rh+ father, and the mother is Rh-, a break in the placental circulation will result in the introduction of fetal Rh positive cells into the maternal Rh negative blood. Iso-immunization may thus be produced and the antibodies thus formed may be transmitted back through the placenta from the maternal circulation into the fetal blood stream. These

antibodies may adversely affect the hematopoietic system of the fetus and produce the condition known as erythroblastosis.

Levine and his associates have tested the blood of over 1000 individuals and have found that, in the general population, 86 per cent of all individuals are Rh positive; 14 per cent are Rh negative. They have also shown that in a group of 111 women who have given birth to babies with erythroblastosis only 9 per cent are Rh positive, while 91 per cent are Rh negative.

The present authors obtained blood from all of the women who had given birth to infants and fetuses in whom there had been at any time a suspicion that erythroblastosis was the cause of death.

Although 86 per cent of the population is Rh positive, isoagglutinins are not ordinarily present in the 14 per cent who are Rh negative. Agglutinins can be produced by the introduction of the Rh antigen into the blood stream.

This introduction can be accomplished either by transfusion or by transfer, during pregnancy, of the Rh antigen from the fetal to the maternal circulation.

When the mother is Rh- and the father is Rh+, either 50 or 100 per cent of the offspring will be Rh positive, the difference in percentage being dependent on whether the Rh factor in father is homo- or heterozygous. If fetal blood containing the Rh factor crosses the placental barrier and gains access to the maternal circulation, agglutinins may be produced in her blood.

If agglutinins are produced either as a result of direct intentional transfusion or by occult transfusion from the fetus, the subsequent introduction of large amounts of blood containing the Rh antigen will result in the agglutination of this newly introduced blood and a fatal transfusion reaction may occur.

When it becomes necessary to transfuse an infant suffering from erythroblastosis, the mother's blood should never be used.

Since the majority of women who give birth to babies with erythroblastosis are known to be Rh negative and may show anti-Rh agglutinins, it is essential to use blood from a known Rh negative donor if it becomes necessary to transfuse one of these women.

Since the Rh factor is present in approximately 86 per cent of the general population, about 12 per cent of all marriages will be between couples where the wife is Rh negative, and the husband Rh positive. It is in this group that the wife is capable of becoming sensitized to the Rh factor and of subsequently reacting on the fetus to produce erythroblastosis. Erythroblastosis, however, occurs in only a small percentage of these women and in the author's experience has been found in only about 0.1 per cent of all pregnancies (The Chicago Lying-In Hospital). To account for the difference between potential and actual incidence, there are several conditions which may contribute: (1) In childless or one-child marriages the limitation in the number of offspring makes the production of erythroblastosis impossible; (2) the Rh antigen in the infant may vary in its ability to stimulate the production of agglutinins in the maternal blood; (3) the ability of the placenta to prevent the passage of the Rh antigen may vary; (4) the maternal response to the introduction of the Rh antigen into the blood stream may vary; (5) the ability of the placenta to permit passage of agglutinins may vary.

In any case where the diagnosis of erythroblastosis is doubtful, support for the diagnosis is obtained by finding the maternal blood Rh negative and the paternal and infant blood Rh positive. If

the mother is Rh positive, the diagnosis of erythroblastosis is less probable.

### Placental Transmission

Placental transmission of sulfathiazole and sulfadiazine, and its significance for fetal chemotherapy is discussed by Speert.<sup>31</sup>

*Sulfathiazole* and *sulfadiazine*, like *sulfanilamide*, diffuse readily across the placenta. Following the intravenous administration of a single 5 Gm. dose of *sodium sulfathiazole* or *sodium sulfadiazine* to the mother during labor, these drugs appear in the fetal blood almost immediately and are retained there in therapeutically effective concentrations for at least six hours in the case of sulfathiazole and considerably longer in the case of sulfadiazine. Equilibrium between maternal and fetal blood is established within three hours. Sodium sulfadiazine results in a higher concentration of the drug in the fetal blood than does an equal dose of sulfathiazole. These drugs appear also in the amniotic fluid, but more slowly than in the fetal blood.

The intravenous maternal injection of sodium sulfathiazole or sodium sulfadiazine is suggested as a method of treating the fetus *in utero* in cases of intercurrent or intrapartum infection caused by susceptible organisms. When the lower genital tract of the mother harbors the gonococcus, the establishment of an adequate sulfathiazole or sulfadiazine concentration in the fetus prior to delivery would appear indicated as a prophylactic measure.

### CONTRACEPTION

The present status of conception control is reviewed by Dickinson.<sup>32</sup>

**Diaphragms and Caps**—Of the two kinds of cover for the cervix, the smaller depends on retention by suction, preferably to the fornices around the projecting

portio. The other provides a partition in the vagina, the upper or anterior pocket holding the cervix, the lower or posterior part providing the channel for the penis. High protection rate depends not a little on the doctor's skill in fitting, as in all office gynecology; doctors outside this specialty (and often within it) need a brief teaching in a birth control clinic, particularly in order to cope with the difficult cases. The diaphragm is unsuited to much damaged or relaxed pelvic floors or to the short (infantile) forms of anterior vaginal wall, all of these preventing the front rim of the device being held well up to the pubic arch. An obese woman with short fingers cannot reach in far enough. There may be objections of psychologic origin.

Bimanual and speculum examinations precede measurement, selection, and fitting. The size of diaphragms most used is 75 (diameter in millimeters, the range from 50 to 105). The diaphragm is fully lubricated with a contraceptive jelly for introduction, plus a near teaspoon in the fold that goes up against the cervix. Leaving the diaphragm in place six or eight hours after ejaculation obviates the need of a douche. If removed soon after coitus, part of the douche precedes taking out and part follows, with due care to distend fully the vaginal passage.

**Jellies and Cream**—The objectives of using such agents are two: blockade of the opening into the cervical canal by adequate viscosity and paralysis of spermatozoa by a spermicide of high efficiency. The average amount used is one teaspoon (5 cc.) injected through a nozzle screwed onto the supply tube after taking off its cap, or drawn into a slender tube syringe that fills from a supply tube.

**Douches**—To distend the vagina so as to open out every fold, the vulvar lips must be held together about the nozzle,

then freed for each successive gush of water. Among household remedies are strong soapsuds, vinegar (two tablespoons to the half pint), alum (a level teaspoon), or lemon juice (a tablespoon to the quart). The effervescent douche directly from the neck of the bottle of the popular cheap carbonated acidulated beverage is much used and is spermicidal.

**Condom**—The condom is the effective mechanical measure most generally available in well-to-do countries. It is suited to those males with a good erection and with strength of feeling tolerating some numbing, to the man taking his share of the responsibility, to the wife careful to douche promptly should it slip off as he makes exit, or in case of break. Practice often lessens objection.

**Withdrawal**—Coitus interrupted just before ejaculation is the contraceptive measure most extensively employed the world over. Its advantages are simplicity and availability with absence of preparation or equipment and complete local contact. Withdrawal is not suited to males unwilling to accept limitation of gratification or for the one man in eight who has quick emission or possibly the few with some sperms in the mucus at the meatus.

**Rhythm or Safe Period**—By avoidance of coitus during the few days in the monthly cycle close to ovulation, control of conception is possible. The difficulty is that there has not yet been discovered any simple means of determining the single day an ovum will receive one of the sperms, which can enter after lying in wait in the tube for about two days. Ovulation occurs about the fourteenth day before the next period is due, but the relative infrequency of regularity in menstruation makes all calculation complicated. Four-fifths of all women vary five days or more in length of cycle, some eight or nine days. Thus, about

ten days preceding the period, the period itself, and the few days close after it show low risk or none, but there are records of conception on every day of the cycle.

With diaphragm and jelly the degree of protection can be expected to register prevention around 90 per cent or from 85 to 95. With the condom, protection ran up to 95 per cent but sometimes was as low as 70.

Withdrawal technic offers a longer range, from 35 to 80.

Of jelly or cream alone there has been insufficient study. An average may be above 80 per cent, between 70 and 90, but the range is wide.

The douche has a variant score, all the way from 16 to 70.

Acceptability presents wide variants and is a factor of weight. In urban private practice in expert hands, 70 per cent were continuing the use of diaphragm and jelly at the end of three years. In birth control clinics 50 per cent carry on with this means after two years, but as few as 30 per cent even in a fine service after three years. For jelly or cream alone continuance after two years ran from 63 to 15 per cent. The return is to previously used methods, such as condom and withdrawal.

## STERILITY

### Amenorrhea

**Treatment by Low Dosage Irradiation**—A follow-up by Mazer and Greenberg<sup>33</sup> for nearly three years of 92 additional cases of amenorrhea, treated by means of *low-dosage irradiation of the pituitary gland and ovaries*, shows that 65 (72 per cent) of the patients have been menstruating normally. It is noted that the data gathered from a long-term follow-up of 165 cases, similarly treated and previously reported, show

permanency of the cures and the safety of the procedure to both the patient and her offspring.

Of the 92 amenorrheic patients in the present group, 54 desired offspring but had not conceived despite the intensive use of organotherapy and other measures for several years. Twenty-eight (54 per cent) of the 54 barren women conceived and carried to term healthy infants; two aborted during the first trimester of pregnancy. All of the 30 women have been menstruating normally since the termination of pregnancy.

Low-dosage irradiation of the pituitary gland and ovaries for the relief of amenorrhea should not be administered without a preliminary pelvic examination and a dependable biologic pregnancy test, unless the patient happened to have menstruated a couple of weeks previously.

A survey of the literature on low-dosage irradiation of the pituitary gland and ovaries, as employed for the relief of amenorrhea, reveals no adverse effects either on the patients or their offspring. Instances of harm recorded in the literature were the result of heavy irradiation, employed in the treatment of uterine fibroids and kindred conditions.

In a discussion of this paper, First stated that for many years he has made a study of the large number of sterility patients who abort within a few months after getting pregnant and of the not too infrequent patient who after a great deal of endocrine therapy goes to term but delivers an abnormal fetus, evidence of so-called low reproductive efficiency or poor germ plasm. Would it not be most illogical to refuse to treat sterility patients because of these remote possibilities? The large number of sterile women who are ultimately delivered of healthy children warrants trying all the means at our command to cure them. By the same analogy one is not justified in fearing to

try low-dosage irradiation, since a higher percentage of blighted ova is to be expected in these women regardless of the type of therapy employed.

### Artificial Insemination

The rôle of artificial insemination in the treatment of sterility is discussed by Guttmacher.<sup>34</sup> The indications for artificial insemination, the author states, are three:

Group A, those cases in which intravaginal coitus between two fertile individuals is impossible because of such mechanical factors as hypospadias, impotence, vaginismus, tumors, or excessive obesity.

Group B, conditions in the female which render successful impregnation difficult—such as retroposed uterus with conical cervix, uterine hypoplasia, uncomplicated anteversion or retroflexion, cervical abnormalities, and endometritis.

Group C, in which the husband is sterile and the wife apparently fertile, or the husband has "cacogenic hereditary characters" which should not be transmitted. Only in Group C must a donor other than the husband be employed.

The author has treated two patients in Group A, using the husband's semen, which was obtained by masturbation; both became pregnant during the second course of intravaginal injections. In 34 cases in Group C in which semen from an unrelated donor was used, 18 women have become pregnant, and five are still under treatment. The author has attempted seven cases of Type B with a total of 33 injections with no success. In artificial insemination of patients in Group C, the semen is introduced 0.5 to 1 cc. inside the external os; intra-uterine injections are not indicated in this group of cases and are apt to cause uterine cramps. If intrauterine injections are to be used, they should be re-

served for cases in which the husband's semen is to be used on the ground that it may "compensate in some doubtful way" for inherent defects in the semen or in the mechanics of impregnation.

**Status**—The status of artificial insemination as a means of overcoming sterility in the barren couple, wherein the male is principally at fault, is analyzed by Folsome.<sup>35</sup>

This procedure, he feels, offers no unusual promise as a panacea in the control of human male sterility, as is evidenced by a review of the available literature. With but one exception, Seymour and Koerner, those results obtained by resorting to artificial inseminations have been little more than mediocre. In the exception noted, Folsome warns the careful reader to review the unique findings with reasonable doubt, for this report, provocative of numerous inquiries anent its analytical reliability, contains numerous discrepancies and is at curious odds with the findings as reported by all others.

The author protests against publication of such extreme claims on the subject of human sterility until these are checked or verified.

Among other things it is of interest to observe in Seymour and Koerner's article that in approximately 9500 children "sired," as the authors term it, by this method, there were no malformations, a less than usual incidence of abortions and ectopics, and, strangely, there is no mention of the usual proportion of twins. As Folsome succinctly states, normal coitus appears less successful than the suggested substitute.

Artificial insemination may have its place in the medical armamentarium in the relief of sterility, although modern research in the physiology of human reproduction indicates that resort to it will become less and less necessary.



### Precoital Douche

The use of a precoital douche of *Ringer glucose solution* in cases of infertility of long duration is strongly recommended by MacLeod and Hotchkiss.<sup>36</sup> They cite 12 successful pregnancies within two to three months of therapy.

The use of the douche was suggested as a result of studies over a period of years at Cornell Medical College on the metabolic behavior of human spermatozoa. In these experiments, the spermatozoa are removed from the seminal fluid by centrifugation and transferred to a balanced salt solution containing glucose. It was found that maximal motility was maintained for many hours at 38° C. in this medium, as long as an adequate supply of glucose was present.

The Ringer-glucose solution was made up as follows: 9 Gm. NaCl, 0.23 Gm. KCl, 0.22 Gm. CaCl<sub>2</sub>, 20 Gm. glucose (C. P.) to 1000 cc. distilled water; 250 cc. to 500 cc. are prescribed as a precoital douche during the fertile period.

The authors emphasize that the efficacy of the technic may be restricted to the type of infertility in which both partners show no striking abnormality.

The possible importance of a seminal pool around the external os aiding in the migration of the spermatozoa from the vagina into the cervix cannot be lightly dismissed. In this sense, any increase in the volume of this pool would be of benefit and, in view of known facts, the authors emphasize that no better diluter could be found than Ringer-glucose solution.

### Endometrial Tuberculosis

Endometrial tuberculosis as a cause of sterility is noted by Rabau, Halbrecht, and Casper.<sup>37</sup> During the last two years they have done endometrial biopsies by means of strip curettage in cases of ster-

ility in order to investigate the development of the cycle in the uterus mucosa and to prove or disprove the existence of normal ovulation. As a result, they have found a considerable number of cases of tuberculosis which had not given rise to any other sign or symptom.

Two hundred and eight endometrial biopsies were carried out. There were 20 cases in which tuberculous endometritis was found microscopically. The main tuberculous changes were epitheloid cell tubercles with giant cells in varying numbers and sometimes conglomerate tubercles. They did not find caseous changes. Frequently tuberculous granulations had penetrated into the lumens of the glands. Secondary nonspecific inflammatory changes were a rule in quite a number of cases.

The uppermost layers of mucous membrane were sometimes studded with numerous tubercles. In spite of the tuberculous changes present, the different stages of secretion and proliferation were fully developed in a high percentage of the cases.

On four women the authors performed a second curettage and examined the material by means of animal experiment and culture. All four cultures and three experiments on animals proved positive for tuberculosis.

In 18 of the 20 positive cases an examination of the lungs could be made, including x-ray examination. There was no evidence of active tuberculosis of the lungs in any of the cases.

The authors feel justified, therefore, in stating that genital tuberculosis plays a much greater part as a cause of sterility than has been supposed up to now.

It still remains undecided whether the endometritis or the salpingitis accompanying it is the cause of the sterility. At any rate, it is not always a question of the patency of the tubes. Tuberculo-

sis endometritis is quite compatible with patent tubes, for insufflation tests in five of the 20 cases which were now positive had formerly shown patency.

## ENDOCRINES

### Physiology

The physiology of the endocrines in pregnancy, lactation, and the puerperium are reviewed by Novak.<sup>38</sup>

**Rôle of Corpus Luteum and Placenta in Pregnancy**—The placenta takes over the chief burden of progesterone production from the corpus luteum at a comparatively early stage of pregnancy, from the late *second* to the *third month*. The pregnandiol excreted probably represents only a small proportion of the endogenous progesterone, although qualitatively it is an index of corpus luteum activity in either the pregnant or nonpregnant woman.

**Influence of Hormones on Uterine Motility**—The spontaneous rhythmic contractility of the uterine musculature is dependent upon the follicular hormone, while progesterone is an inhibitor of this contractility. The dilatation of the ureters seen so often in the late stages of pregnancy may be due to the relaxing action of progesterone upon the smooth muscle.

**Probable Rôle of Hormones in Initiation of Labor**—The determining forces in parturition would seem to be: (a) Removal of certain inhibiting factors; (b) the addition of certain positive factors promoting expulsive contractions; (c) both. Of the first group, progesterone would seem to be most important. Of the second group, the follicular hormone and the oxytocic principle of the posterior pituitary are responsible.

**Rôle of Hormones in Mammary Development and Lactation**—Estrogen has been believed to furnish the hormonal stimulus for the proliferative

growth of the duct system, and progesterone for the acinary and lobular development of the breast tissue. Neither estrogen alone nor estrogen plus progestin will stimulate mammary growth in the hypophysectomized rat, while anterior pituitary material does induce both duct and lobule-alveolar growth in such an animal. There is, therefore, a pituitary-mammogen theory of mammary-gland growth, according to which "estrogen stimulates an increased secretion by the anterior pituitary of a duct-growth factor, while progestin plus estrogen causes an increased secretion of a lobule-alveolar growth factor by the pituitary."

The chief discussion of recent years has revolved about the question of why lactation does not occur during pregnancy, and what the factors are which initiate it several days after parturition. Four views have been offered by way of explanation: (a) The placenta produces a suppressing agent during pregnancy which holds lactation in check; (b) the mechanical distention of the uterus by the fetus and placenta inhibits lactation; (c) the secretion of progesterone by the corpora lutea suppresses lactation during pregnancy, and (d) during pregnancy the comparatively large amounts of estrogen present in the blood stream inhibit the lactation process.

The lactogen content of the pituitary remains low throughout pregnancy, but increases from two- to four-fold following parturition. These findings indicate that lactation fails to occur during pregnancy for the reason that the lactogenic hormone is inadequate to support lactation. Some as yet unknown factor is responsible for the increased production of lactogen after parturition.

One questions the validity of reported observations upon the human female tending to indicate inhibition of lactation by estrogens or androgens, one obvious

objection being that the infants were taken from the breasts when such therapy was begun, this in itself furnishing an adequate explanation of cessation of milk production. When suckling was permitted to continue, lactation was not prevented by *stilbestrol* in doses as high as 500 mg.

A sharp distinction is to be drawn between painful engorgement of the breast and the onset of lactation. Pregnant and puerperal women are extremely tolerant to *stilbestrol*, large doses of from 250 mg. a day to 1500 mg. a week producing no harmful effects. The act of suckling does not appear to be essential for initiation of lactation, its importance being rather in the later maintenance of that function.

**Menstruation and Ovulation During Lactation**—The occurrence of pregnancy during lactation amenorrhea indicates merely fertilization of an egg from a first ovulation. If the fertilization had not supervened, the ovulation would have been followed by menstruation.

### Therapy

Endocrine therapy in obstetrics is reviewed by Hamblen.<sup>39</sup> The various hormonal agents used in gynecology and obstetrics may be grouped into two general categories: (1) Crystalline steroids which comprise hormones of the gonads and adrenal cortex or their derivatives, and certain nonhormonal synthetic chemicals with endocrinelike properties; (2) extracts of protein or proteinlike nature derived from the pituitary and thyroid glands and from certain body fluids.

There are four groups of steroid hormones: estrogens, androgens, progestational steroids, and adrenal cortical steroids.

**Estrogens—Therapy During Pregnancy and the Puerperium**—The indications for estrogenic therapy during the course of pregnancy in general are not

clear-cut. Estrogens have been used in the treatment of pregnant women having histories of repeated abortions and also in the treatment of threatening abortions. They have been employed also in eclamptic and toxemic states. Estrogenic therapy has been employed in nausea and vomiting of pregnancy and for hastening of labor. The rationale for their use in these conditions is based on the presumed existence of an estrogenic deficiency.

In eclampsia and abortion patients, estrogenic therapy has been combined with the concomitant administration of *progesterone*. *Sodium pregnandiol glucuronide*, an inactive metabolic of progesterone, administered in daily doses of 100 mg., is said to enhance the activity of *estradiol benzoate* and progesterone in the treatment of eclampsia.

Many obstetricians choose to stop lactation or decrease milk formation in the case of painful engorgement of the breast by means of estrogenic therapy. Recently, *diethylstilbestrol* has replaced the limited use of natural estrogens in this procedure. Its action is fast, and its toxic manifestations, however slight they may be under other circumstances, are absent in the puerperal woman. The optimum daily dosage seems to be 5 mg. As a rule, only a few days of therapy are required for the lactating tissues to become inactive.

**Progestational Principles** — Numerous reports have cited the efficacy of *progestin* in preventing abortion; 5 to 10 mg. should be given daily. Progestin often has received credit for success when the effects of adjuvant measures, such as *thyroid substance*, *bed rest*, *limitation of sexual and other activities*, etc., have not been evaluated. The author has not been impressed particularly with progesterone therapy in these conditions. When pregnant women show definite evidence of deficiency in

the progestational principle, *i. e.*, decreased pregnandiol values of the urine, even the most intensive progesterone therapy fails to prevent abortion.

The use of **progesterone** therapy for afterpains is based on its presumed uterine quieting effects. It has been described as being of benefit in this condition although other and much cheaper methods have proved quite effective in years past.

**Adrenal Steroids — Corticosterone** and its related steroids may permit worthwhile applications in obstetrics by virtue of acetate of desoxycorticosterone, the most widely used of these cortical steroids. It is not a complete cortical principle, however, since it lacks the carbohydrate metabolic factor.

**Desoxycorticosterone acetate** may be of value in treating those patients who have become markedly dehydrated and depleted of sodium and chloride due to pernicious vomiting of pregnancy. It has been suggested the dosage be small, 1 or 2 mg. daily, and that overtreatment be avoided. Extracts of adrenal cortex have been used also in vomiting of pregnancy. The glucose mobilizing effects of these may be of value.

**Stilbestrol**—The use of **stilbestrol** in obstetrics is discussed by Abarbanel, Aranow, and Goodfriend.<sup>40</sup> The relief of painful engorgement of the breasts in the puerperium is one of its chief uses in obstetrics.

1. *Prevention (in Nonnursing Mothers)*—An adequate uplift breast support is first adjusted on the patient. On the day after delivery, 10 mg. of **oral diethyl-stilbestrol** is given followed by 5 mg. daily for three to five days, then 3 mg. daily for three days, and finally 1 mg. daily for three to six days. By spreading the dose schedule out over a period of about two weeks while gradually decreasing the dosage, the incidence of delayed filling of the breasts may be

considerably reduced. If therapy is not started within 48 hours after delivery, the initial dose should be 25 mg. Delayed filling of the breasts may occur some two to 12 or more days later. As a rule, it is transitory and painless, while secretion is usually slight and watery. In the manner just outlined, good results were secured in close to 90 per cent of the patients.

2. *Prevention in the Nursing Mother* (especially primiparas) : Beginning right after delivery, 5 mg. of diethylstilbestrol are given daily for three to five days. Since actual milk secretion does not usually occur until the third or fourth day postpartum, it is an excellent idea not to put the baby to breast until then, thus avoiding many a cracked or fissured nipple. Adequate milk secretion will occur if the baby continues to nurse vigorously.

3. *Prevention After Weaning*—After an adequate uplift breast support has been applied, the patient is given 25 mg. of diethylstilbestrol orally. The next day 10 mg. is administered, followed by 5 mg. daily for the next three days.

4. *Relief of Painful Engorgement After Its Onset*—After an adequate uplift breast binder is applied, 25 to 50 mg. of diethylstilbestrol are given orally. Relief may be apparent in 18 to 24 hours in about 65 per cent. The next day 10 mg. are administered orally, followed by 5 mg. daily for three days. In about 25 per cent, secondary filling may occur, while a watery secretion may persist for several days or even weeks. In contrast, when 10 to 25 mg. of **testosterone propionate** are given by injection, or 100 mg. of **methyl testosterone** are given orally, relief is usually apparent in two to 12 hours in close to 90 per cent, while secondary filling is rarely, if ever, noted.

5. *Inhibition of Lactation and Suppression of Established Milk Secretion*—Diethylstilbestrol will not inhibit the normal onset of lactation, although it will

delay the appearance of the normal average amount of milk secretion until two to seven days after the drug is stopped, provided the baby continues to nurse. Once lactation is established, however, as much as 500 mg. of diethylstilbestrol will not materially affect the amount of milk secretion.

In *threatened abortions*, Karnaky<sup>41</sup> gives five 5 mg. (25 mg.) *diethylstilbestrol* tablets every 15 minutes until the pain and bleeding stop, then two 5 mg. tablets every hour for six doses, then one 5 mg. tablet every hour for six doses, and then 10 mg. every night until the eighth month. The dosage determines the effect. Small amounts produce proliferation of the endometrium and large doses inhibit the pituitary oxytocins on the uterine musculature, regulate the endometrial vascular system by keeping the spiral arteries dilated, and stimulate natural progesterone production, which helps to complete the changes in the endometrium, which he thinks is one of the most important functions of the progesterone. They also inhibit the excess production of gonadotropin of the anterior pituitary, cause normal rhythmic contractions of the uterus, and aid in the normal metabolism of progesterone and estrogens to estrone and estriol. He believes that diethylstilbestrol will replace *corpus luteum* for the treatment of threatened and habitual abortions and premature labor.

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## MEDICINE

*Edited by* GEORGE MORRIS PIERSOL, B.S., M.D., AND EDWARD L. BORTZ, A.B., M.D.

### AVIATION MEDICINE

LOUIS HOPEWELL BAUER, A.B., M.D.

The war has increased tremendously the interest in aviation medicine. Old problems have become more important and new problems have developed. Altitudes for operational flights have greatly increased and speeds attained have exceeded any previous speeds.

**Flying Aptitude**—Considerable attention has been paid to the subject of flying aptitude. Liljencrantz<sup>1</sup> has stated, "Fitness for service in modern naval aviation must include high tolerance for the conditions attendant upon prolonged high altitude flight, namely, low oxygen tension, reduced atmospheric pressure, rapid reduction in atmospheric pressure, and low temperature. Also the ability to withstand high acceleration and fatigue is a prerequisite."

He stated that in spite of high physical standards, 25 per cent of those who meet these standards fail in flight training, and that personality defects rather than physiological ones are responsible for many of these failures.

Since he wrote this, it is understood that both the Army and Navy have been able to increase materially the results of aptitude selection. This has been done by psychological tests and biographical studies of the applicant. The methods are at present secret and cannot be published until after the war.

**Dark Adaptation**—In a study of dark adaptation and the importance of avitaminosis to that function, Flynn<sup>2</sup> studied 500 pilots and evolved a test for dark adaptation. He states that the test attempts to simulate the light involved in flying over territory at night in a bomber, the ability of the crew to look from a

lighted cockpit suddenly to the dark world below and to pick up a faintly lighted target—this involving the ability of the pilot to adapt his eyes to the dark and taking into consideration the short interval of time available on these missions. He also found that 6.4 per cent of these pilots were deficient in vitamin A, even when fed a diet containing an abundance of vegetables. He claims to have treated two-thirds of these deficient pilots successfully with large doses of vitamin A. Yudkin<sup>3</sup> found that alcohol and benzedrine both produce transient improvement in dark adaptation without any corresponding rise in blood vitamin A; the degree of temporary improvement so produced may even exceed that possible with vitamin A. Vitamin C he did not find improved dark adaptation.

**Airsickness**—Rubin<sup>4</sup> made a study of air sickness and its relation to progress in flying training. He concluded that 11 per cent of all aviation cadets become sick during their primary flying and that 52 per cent of these were eliminated. If they became airsick during the first nine days of their training, then 69 per cent were eliminated. The later they became airsick during their training, the better chance they had of being able to complete their course. He came to the conclusion that the most important causes of airsickness during primary training are psychogenic.

**Aviation Accidents**—Herbolzheimer<sup>5</sup> made a study of 300 non-selected aviation accidents and found that it was reasonable to conclude that pilots with impairments could be expected to be involved in accidents more

frequently than persons with no impairments. The accident rate, he found, was one-third greater in the physically defective group than in the normal group. Eighty-five per cent of the accidents were due to pilot error and 15 per cent to engineering reasons. He feels that further study should be made of the pilot error group and that they should be separated into three classes: (1) The pilot is not adapted to flying—by temperament or otherwise unable to function properly under all conditions; (2) the pilot, by insufficient training or practice, fails to react properly under circumstances in which a better trained pilot would be able to do so; and (3) circumstances under which no pilot could be expected to succeed. The first is a matter of selection, the second a matter of supervision of training, and the third a matter of regulation only.

**Cold**—In a study of protection of the crew against cold, Pinson and Benson<sup>6</sup> state that the best solution at present is to incorporate the best features of the electrically heated suit with the use of insulative clothing of maximum bulkiness commensurate with normal personal comfort and efficiency. They recommend the standard intermediate winter flying clothing, electrically heated, and with the addition of heavy mittens.

**Altitude**—There having been some controversy over the question of whether or not discontinuous exposure to anoxia produces acclimatization, Stickney and Van Liere<sup>7</sup> decided to study the matter further. They experimented with dogs and concluded that discontinuous exposure to anoxia is capable of producing a noticeable degree of acclimatization, the degree, as measured by the amount of hemoglobin and the number of red blood cells, being directly proportional to the severity of the anoxia and the length of the exposure. No further work has been

reported on aviators. As the authors point out, if aviators do become acclimatized, they should show an increase of "ceiling." How practical the matter is, however, is questionable as all aviators must wear masks above certain levels and on flights to very high levels must inhale oxygen from the ground up.

It has been suggested that the addition of carbon dioxide to oxygen might increase the tolerance of individuals to extremely high altitudes. It is known that above 35,000 feet there is a rapid fall in the oxygen saturation of arterial blood and that at 42,000 feet the subject breathing 100 per cent oxygen is in the same situation as the subject at 18,000 feet breathing atmospheric air. Barach *et al.*<sup>8, 9, 10</sup> have studied the matter further in experiments on dogs. They came to the conclusion that addition of carbon dioxide corresponding to a tension of 14.3 mm. Hg. increased the minute ventilation by 39 per cent without any beneficial influence on the oxygen tension of the mixed venous blood.

They also found no evidence that the sea level equivalent of two per cent carbon dioxide when administered with oxygen had any advantage on cerebral oxygen tension at a simulated altitude of 38,000 feet.

On the other hand, Gibbs *et al.*<sup>10</sup> feel that "the addition of carbon dioxide to low oxygen mixtures permits maximal utilization of the available oxygen because of: (a) Increased pulmonary ventilation and consequent increased oxygenation of the arterial blood; (b) peripheral vasoconstriction and cerebral vasodilation, insuring to the brain a maximal share of the circulating blood, and (c) shift in the hemoglobin dissociation curve so that the blood unloads a greater proportion of its oxygen in the tissue."

With the high incidence of malaria among our fighting forces, the effect of



antimalarial agents on altitude tolerance becomes important. Van Liere and Emerson<sup>11</sup> reported that quinine, atabrine, and plasmochin had no appreciable effect on tolerance of mice to lethal effects of anoxic anoxia even when given repeatedly.

In a discussion of the importance of indoctrinating flying personnel with the physiologic effects of high altitude and the need for oxygen, Carson<sup>12</sup> has summarized the effects of altitude briefly. He states that there are 3 main stresses on the flyer's physiologic adaptive mechanism. In the order of their importance, he lists them as: (1) The difficulty of maintaining an adequate oxygen supply under the very low barometric pressures obtained at altitudes above 35,000 feet; (2) the damaging effects of nitrogen elimination from blood and tissues in the form of bubbles and air emboli, causing aeroembolism; and (3) the coincident effect of extremely low temperatures tending to exaggerate the effects of the first two. He invites attention to the fact that symptoms of acute anoxia may develop suddenly and insidiously between 10,000 to 15,000 feet. Further, even as low as 12,000 feet, nitrogen may begin to escape in the form of minute bubbles, and when 30,000 feet is reached definite symptoms of aeroembolism may develop in susceptible individuals.

Experimental work on animals has revealed, post mortem, blocking of terminal blood vessels by air emboli, hemorrhages in certain viscera, and marked hemoconcentration. Also, damage to the cord and nerve tissue has been noted.

He emphasizes the fact that there are individual differences in the tolerance to anoxia and that these differences offer a basis of classification of personnel. For example, if a subject develops symptoms of aeroembolism at 28,000 feet, he will be apt to develop more severe symptoms

at higher altitudes and should be restricted to moderate altitude flying.

Barach *et al.*<sup>13</sup> found in experiments on rats that preoxygenation before exposure to high altitudes decreased mortality. In a group of 91 controls, exposed to a simulated altitude of 55,000 feet, 34 died, while in a group of 90 which had been preoxygenated before exposure to the same altitude only 11 died. Autopsies showed marked abdominal distention with lifting of the surrounding skin and congestion of the lungs, whereas in the preoxygenated group, there was only slight distention of the abdomen and slight or moderate pulmonary congestion.

**Transportation of Patients by Air**—A great deal of experience has been accumulated during the present war in the evacuation of sick and wounded by air. Patients can be brought to hospitals more comfortably and quickly where they can receive definitive and adequate treatment. Not only has it reduced mortality but it has served as a definite boost to the morale of the wounded soldier to know that he can be quickly transported to a base hospital. More and more civilian patients are also being transported by air. Certain types of cases do not lend themselves well to air transportation. Lovelace and Hargreaves,<sup>14</sup> and later Tillisch, Statler and Lovelace,<sup>15</sup> have reported at length on this subject. They state that persons with well-compensated heart disease may fly at altitudes now flown by commercial aircraft if oxygen is used. However, those with severe valvular disease, easily provoked angina pectoris, or who have recently had congestive failure, and the old and feeble, should not fly.

Pneumothorax patients should not fly because expansion of the lung or of the air in the pleural cavity, may spread infection, cause hemorrhage, or tear adhesions. As a general rule, asthmatic

patients should not fly. Penetrating wounds of the abdomen or perforated viscera are contraindications to flying also, because expansion of the intestinal gases may force the organs out through the opening or carry fecal matter into the peritoneal cavity, although in perforations of the gastrointestinal tract the use of Wagensteen drainage may keep the organs decompressed.

Patients treated with sulfonamides should have oxygen. Patients with acute or recent upper respiratory infections, acute sinusitis, or middle ear conditions should not be exposed to marked or sudden changes of atmospheric pressure because of the danger of spreading the infection.

Persons with a recent cranial operation or who have had a recent spinal tap should not fly.

Patients suffering from shock should be treated for the shock before flying.

**High Speed and Deceleration**—Speeds are constantly increasing and various workers have endeavored to find means of protection against the dangers of deceleration. Inflatable abdominal belts, changes of posture for the

pilot, and drugs have all been used. While a great deal of experience is being accumulated and progress being made, nothing dramatic will be published, probably, until after the war.

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## CARDIOVASCULAR SYSTEM

ALBERT W. BROMER, A.B., M.D.

### CORONARY ARTERY DISEASE

#### Coronary Occlusion

**Blood Pressure Before, During and After Coronary Occlusion**—A study by Master, Jaffe, Dack, and Silver<sup>1</sup> of the blood pressure of 538 patients (416 males and 122 females) before, during, and after coronary occlusion has revealed a fall of blood pressure during the attack in every instance. The rapidity and degree of fall varied con-

siderably. Slightly over half of the attacks were initial and the remainder were second or third episodes. Recovery occurred in 383 cases (71 per cent), 205 of which were followed through a period of one to seven years. At least 69 per cent of the patients had hypertension before the attacks.

The criteria for the presence of hypertension before the attack were: (1) A systolic pressure of 150 mm. or more at any time during observation; (2) a di-

astolic pressure of 96 mm. or more prior to the attack; (3) a diastolic pressure of 90 mm. or more during or after the attack, and (4) marked enlargement of the heart without obvious cause. Hypertension was more frequent with multiple than with initial attacks, and in women than in men. Sixty-four per cent of the men and 80 per cent of the women had an elevated blood pressure at one time or another. The frequency of hypertension increased with age.

Fifty-seven per cent of the patients showed a rapid fall of blood pressure, that is, in the first three days the blood pressure fell to a level approaching the lowest pressure during the attack. In 44.5 per cent the fall was gradual, reaching a low level in one to three weeks. In some cases the initial fall was soon followed by temporary or permanent rise in pressure. In general, the diastolic pressure followed the same trend as the systolic, but the fall in the former was usually less precipitate and less marked than that in the systolic. This resulted in a decrease in the pulse pressure, often to as low as 10 to 20 mm. Infrequently, the onset of coronary occlusion with severe pain was associated with a transi-

tory rise in blood pressure which sometimes reached 200 mm. systolic.

The trend of the blood pressure was similar in the hypertensive and non-hypertensive groups, although a rapid fall was more common among the non-hypertensive patients who died. The systolic blood pressure rarely fell below 90 mm. in the hypertensive group, but this was common in the nonhypertensive group. When the pressure did fall below 80, death usually occurred. In almost one-fifth of the patients with a previous pressure of 200 mm. or more the fall was not below 150 mm. Two-thirds of the hypertensive patients regained a hypertensive level; in half of them it occurred before discharge from the hospital, and in the remainder usually within one or two years. The height of the blood pressure after the attack did not significantly influence the incidence or severity of angina pectoris, or the frequency of subsequent attacks of coronary occlusion or of heart failure.

### Angina Pectoris

**Prognosis**—In a follow-up study by White, Bland, and Miskall<sup>2</sup> of 497 cases of angina pectoris (377 males and 120

TABLE 1.  
SUMMARY OF DATA ON THE 497 PATIENTS WITH ANGINA PECTORIS.

	<i>Total (497)</i>	<i>Dead Within 3 Yrs. (100)</i>	<i>Living 14 Yrs. or More (52) (3 deleted)</i>	<i>Total Dead (445)</i>
Sex:				
Male.....	377 (75.9%)	81 (81%)	36 (69.2%)	340 (76.4%)
Female.....	120 (24.1%)	19 (19%)	16 (30.8%)	105 (23.6%)
Age at onset, average.....	56.5	59	51	
Limits.....	20-80	24-80	38-72	
Age at death, average.....	.....	.....	.....	65.8
				Males, 64.3
				Females, 67.4
				7.9
Average duration of life.....	9.06 (to date)	.....	18.4	Males, 7.58
				Females, 8.91

females) that were first observed in the years from 1920 to 1930, 445 were found to have died and 52 to be still living (Table 1). The average duration to death of the 445 was 7.9 years, while the average duration from onset of the disease in the living was 18.4 years. The average duration for the combined dead and living was 9.0 years, which, when all the present survivors succumb, will ultimately increase without doubt to a figure approximating 10 years, a duration of life about double that at present widely regarded as the expectation of life after the first appearance of angina pectoris.

Seventy-six per cent of the deaths were due to cardiac causes. Approximately one-fifth of the entire group had normal cardiac examinations, blood pressures, and electrocardiograms at the time of the first examination, and these patients as a rule lived longer. Features such as hypertension, myocardial infarc-

tion, cardiac enlargement, abnormal heart sounds, congestive heart failure, and abnormal electrocardiographic findings occurred much more frequently in the group that died within three years than in those living 14 years or more (Table 2). A pronounced degree of nervous sensibility was a favorable influence. The more stolid, phlegmatic person usually has more advanced disease before he feels it, pays less heed to the subjective manifestations of coronary insufficiency, and is more apt to overstep his physical limitations.

Angina pectoris decubitus was found in 103 (20.6 per cent) of the 497 cases. There were no significant differences in the average duration of the disease to death or in the living between this group and that of the group as a whole. The average duration to death in 98 of the 103 patients was 7.6 years—only a shade less than the 7.9 years average for the 445 dead patients of the series. Five of

TABLE 2.

ANGINA PECTORIS: COMPARISON OF DATA OBTAINED ON OUR FIRST EXAMINATION ON THE GROUP OF 497 PATIENTS AS A WHOLE WITH DATA ON 100 DYING WITHIN 3 YEARS AND WITH DATA ON 52 PATIENTS STILL LIVING 14 YEARS OR MORE SINCE ONSET.

	<i>Total (497 Patients)</i>	<i>Dead Within 3 Yrs. (100 Patients)</i>	<i>Living 14 Yrs. or More (52 Patients)</i>
Hypertension.....	182 (36.6%)	42 (42%)	7 (13.4%)
Myocardial infarction.....	205 (41.2%)	54 (54%)	13 (25.0%)
Cardiac enlargement.....	337 (67.8%)	83 (83%)	21 (40.3%)
Abnormal heart sounds.....	226 (45.4%)	56 (56%)	15 (28.8%)
Congestive failure.....	77 (15.5%)	22 (22%)	0
Abnormal electrocardiogram..... (393 patients were electrocardiographed)	117 (29.7%)	32 (32%)	9 (17.3%)
Normal cardiac examination.....	74 (18.8%)	9 (9%)	18 (34.6%)
Nervous sensibility pronounced.....	239 (48.0%)	40 (40%)	34 (65.3%)
Severity of pain:			
Uncertain.....	13 (2.6%)	4 (4%)	1 (1.9%)
Mild.....	129 (25.9%)	24 (24%)	21 (40.0%)
Moderate.....	151 (30.4%)	31 (31%)	19 (38.4%)
Pronounced.....	104 (20.9%)	18 (18%)	6 (11.5%)
Severe (decubitus).....	103 (20.7%)	23 (23%)	5 (9.6%)

the 52 patients living 14 years or more had this type of pain—with an average duration of 18.2 years.

In a supplementary series of 75 cases with angina pectoris decubitus (56 males and 19 females), life was relatively short after the onset of the decubitus type of pain, averaging 2.8 years in 47 cases followed to death (Table 3). The duration of the precedent angina of effort, however, brought the overall average duration of life close to that of the larger group. Gross myocardial infarction recognizable clinically followed angina pectoris decubitus within 24 hours in 22 (29 per cent) of the 75 cases and within a period of three months in 19 (25 per cent) others.

The findings in this study do not warrant the conclusion that patients with angina pectoris live longer than formerly; in all probability they are merely a more accurate estimation of the prognosis as it has always existed—accomplished through a long time follow-up of a large group of patients throughout the entire course of the disease. Treatment, consisting in the main of more careful living over the periods of greater degrees of coronary insufficiency, however, also may have exerted a favorable influence. The conception of the frequent acute-

ness or subacuteness of coronary insufficiency, with appreciation of the natural tendency for the development of an adequate collateral coronary circulation, is of great significance both in prognosis and in treatment.

**Treatment**—In an objective evaluation of the efficacy of treatment of angina pectoris carried out over a ten-year period, Riseman<sup>3</sup> has found that 27 per cent of patients respond well to practically all available forms of therapy, 33 per cent respond to a moderate degree, and 40 per cent usually fail to respond appreciably. The value of each form of treatment was determined by use of an exercise tolerance test consisting of mounting and descending a two-step staircase repeatedly under constant conditions, *viz.*, (1) a room temperature of 45° to 55° F.; (2) one hour after a light meal; (3) no recent attack; (4) no medication, and (5) familiarity with the test. An increase in exercise tolerance of 100 per cent or more following treatment usually is associated with complete or almost complete freedom from attacks in daily life; an increase of 30 to 75 per cent, with a moderate diminution, but not complete disappearance of attacks, and an increase of 20 per cent or less is usually unassociated with any clinical

TABLE 3.  
ANGINA PECTORIS DECUBITUS.  
75 Additional Cases Observed from 1923 to 1943.

	Total	Males	Females	Dead	Living
Number . . . . .	75	56	19	47	28
Average age at onset of angina of effort or decubitus . . . . .	57.9	57.1	60.7		
Limits . . . . .	....	37-79	46-79		
Average age at death . . . . .	63.9	62.2	68.6		
Limits . . . . .	....	44-84	52-82		
Average duration to death after development of:					
(1) Angina of effort . . . . .	5.6	5.2	6.7		
(2) Angina decubitus . . . . .	2.8	2.4	3.8		

TABLE 4.  
COMPARATIVE VALUE OF METHODS OF TREATMENT.

Type of Therapy	Degree of Value		
	Marked	Moderate	None
Nitrites	Nitroglycerin, 1/100 gr. Nitroglycerin, 1/500 gr. Octyl nitrite Amyl nitrite	Erythrol tetranitrate, ¼ gr., 4 times daily Mannitol hexanitrate, 1 gr., 4 times daily	Sodium nitrite, 1 gr., 4 times daily
Purines	Theobromine and sodium acetate, uncoated, 7½ gr., 4 times daily Theophylline and sodium acetate, uncoated, 3 gr., 4 times daily Theophylline and calcium salicylate (Phyllicin), 8 gr., 4 times daily Theobromine sodium ace- tate, enteric-coated, 7½ gr., 4 times daily Aminophylline, 3 gr., 4 times daily Theophylline methyl gluca- mine (Glucophyllin), 4 7/10 gr., 4 times daily	Theophylline, 4 gr., 4 times daily Theobromine, 5 gr., 4 times daily Theobromine and sodium sa- licylate (Diuretin), 7½ gr., 4 times daily Theobromine and calcium sa- licylate (Theocalcin), 15 gr., 4 times daily Theophylline diethanolamine (Deriphyllin), 1 cc., 4 times daily Theophylline monoethanola- mine (Theamin), 3 gr., 4 times daily	Caffeine citrate, 2 gr., 4 times daily Theobromine and calcium-glu- conate (Calpurate), 15 gr., 4 times daily
Sedatives	Phenobarbital, ½ gr., 4 times daily Codeine sulfate, ½ gr., 4 times daily Cobra venom, intramuscu- larly	Theamin with amytal, 3¾ gr., 4 times daily Theominal, 5½ gr., 4 times daily Dilaudid, 1/20 gr., 4 times daily Bed-rest for 6 weeks	Papaverin, ½ gr., intrave- nously
Cinchona derivatives	Quinidine sulfate, 5 gr., 4 times daily Quinophylline (quinidine sulfate, 5 gr., and amino- phylline, 3 gr.), 4 times daily	Quinine sulfate, 5 gr., 4 times daily	
Procedures or drugs acting on the auto- nomic nervous sys- tem	Pressure on the carotid sinus Atropine sulfate, 1/120 gr., 4 times daily	Physostigmine salicylate, 1/40 gr., 4 times daily Amphetamine (Benzedrine) sulfate, 1/12 gr., 4 times daily	X-radiation of adrenal glands X-radiation of thoracic sym- -pathetic nerves Novatropine, 1/12 gr., 4 times daily Syntropan, 1½ gr., 4 times daily
odides and intrave- nous saline solution	Potassium iodide, 1 Gm. enteric-coated tablets, 3 or 4 times daily	Normal saline solution, 500 cc. intravenously, daily Sodium chloride, 5% solution, 200 cc. intravenously, daily Sodium iodide, 5% solution, 200 cc. intravenously, daily	Potassium iodide, saturated so- lution, 15 drops, 3 times daily Lugol's solution, 15 drops, 3 times daily
Surgical	Total thyroidectomy Paravertebral injection of alcohol		Denervation of thyroid gland
Miscellaneous	Heat	Inhalation of oxygen during exercise Whiskey, 1 oz. before work Metrazol, 3 gr., 4 times daily Inhalation of trichlorethylene	Lactose Sodium bicarbonate, 5 gr., 4 times daily Calcium salicylate, 5 gr., 4 times daily Ethylene diamine hydrochlor- ide, 1 gr., 4 times daily Coramine, 1 teaspoonful, 4 times daily Myorgal, 2 tablets, 4 times daily Depropanex, 2 cc., daily Dinitrophenol, 25 mg., 4 times daily Cigarette smoking Estrogenic substances, 10,000 I. U., daily Testosterone, 25 mg., daily Thiamine, 10 mg., 4 times daily Niacin, 50 mg., 4 times daily Kerr abdominal belt Digitalis Theophyllinated genin of squills

improvement. Of the 68 methods of therapy evaluated, 20 were found to be of considerable value, 22 were of slight value, and 26 were of psychologic value only (Table 4).

Individualization is required in the treatment of angina pectoris. Careful observation may reveal specific precipitating factors, such as walking up hill or after meals, going out into the cold, or emotional disturbances, that can be guarded against or eliminated. A change in habits, the use of sedatives, or the prophylactic use of nitroglycerin at appropriate times frequently proves of value. In a few cases (less than 1 per cent) hyperthyroidism, anemia, polycythemia, or arrhythmias responsible for attacks may be discovered and corrected. As a rule, medication is necessary.

The purines are most likely to be of value. *Theobromine sodium acetate, enteric-coated*, 0.5 Gm. ( $7\frac{1}{2}$  grains), four times daily, is the drug of choice. *Theophylline sodium acetate*, 0.2 Gm. (3 grains), and *theophylline calcium salicylate*, 0.5 Gm. ( $7\frac{1}{2}$  grains), are equally helpful but more costly. *Aminophylline*, 0.2 Gm. (3 grains), is somewhat less efficacious, and also is more expensive. In using the enteric-coated preparations, it must be borne in mind that several hours elapse before effect begins. For example, the dose administered before retiring at night is effective the following morning; in many cases, therefore, it is well to give in addition a single dose of *nonenteric-coated purine preparation* on the patient's arising. Purine preparations proved of benefit in 43 per cent of all cases. During the first few weeks of therapy, or if the symptoms are severe, it may be advisable to give 0.00016 Gm. ( $\frac{1}{400}$  grain) of nitroglycerin under the tongue every hour when the patient is awake. Sedatives may be given as an adjunct—to

help stabilize the patient emotionally. If this regimen is of value, attacks in daily life will disappear completely or almost completely within a week.

If no satisfactory response is obtained with purine preparations, *quinidine sulfate*, 0.324 Gm. (5 grains), three or four times daily may be substituted. Quinidine is about as effective as the purines, and the toxicity in patients with angina pectoris and normal cardiac rhythm is low. Sixty-one per cent of all patients were benefited by the purines or quinidine. The treatment of the remaining two-fifths is a difficult problem. *Atropine sulfate*, 0.0005 Gm. ( $\frac{1}{120}$  grain), four times a day; *potassium iodide* in comparatively large doses—1.0 Gm. (15 grains)—in an enteric-coated tablet, three or four times daily, and sedatives, especially *codeine sulfate*, were of some value.

In severe angina pectoris, a combination of therapeutic agents may be required. Such patients should have a period of complete bed rest combined with adequate sedatives and small hourly doses of *nitroglycerin*. In some cases it is advisable to give in addition adequate doses of a *purine* and, if necessary, *quinidine sulfate*. This regimen usually results in the complete disappearance of pain within a week, unless there has been a recent coronary occlusion or a strong emotional element is present.

In cases with recurrence of symptoms on return to normal activity, *cobra venom* is worthy of a trial. This drug diminishes attacks without affecting the underlying cardiac mechanism responsible for the pain; it is given by injection daily for at least a week and two or three times weekly thereafter. Surgical treatment should be considered only when other measures fail to give relief. *Total thyroidectomy* has given more striking results than any other form of



surgical treatment; it is the procedure of choice in patients with normal basal metabolic rates, prolonged but nonprogressive symptoms, and a fair life expectancy, who are adequate surgical risks. In patients not suitable for total thyroidectomy *paravertebral injection of alcohol* may be used, although it rarely results in an increase in exercise tolerance and may be followed by neuritis. The comparative freedom from pain that occurs in some instances, however, justifies its use in the few selected patients who may require such relief.

## ELECTROCARDIOGRAPHY

### Standardization of Electrocardiographic Nomenclature

The nomenclature employed by Einthoven to designate the individual components of the electrocardiogram has served its purpose well, in spite of the tremendous growth of the science of electrocardiography. With the advance of knowledge the terms and symbols have been utilized to meet new needs and have acquired meaning which they did not originally possess and which are not exactly the same for all workers. To avoid misunderstanding, the Committee of the American Heart Association on the Standardization of Electrocardiographic Nomenclature has redefined the terms that are in general use,<sup>4</sup> for it is believed that the introduction of new terms would be more confusing than helpful.

Each electrocardiographic component has a characteristic contour and a distinctive relation to other events of the cardiac cycle. It is clearly desirable that deflections alike in origin always be given the same name, and that deflections unlike in origin bear different names. The first electrocardiographic component (P) is held to represent all those electrical forces produced by de-

polarization (activation) of the auricular muscle; the second ( $T_a$ ), all those electrical forces produced by repolarization of the auricular muscle. The third (QRS) and fourth (T) components are held to represent all the electrical forces generated when these same physiochemical changes take place in the ventricular myocardium. The last (U), which is less well understood, apparently depends upon some sort of readjustment of the polarization of the ventricular muscle. Since these physiochemical changes are closely related to the mechanical activities of the heart, and necessarily occur whenever the heart beats, their electrical representatives can never be actually absent in any lesion. Some, however, may be isoelectric or of such low voltage as to be imperceptible, and often a small deflection is difficult or impossible to detect because it is superimposed upon a much larger one.

The recommendations of the Committee are as follows:

"1. The symbols P,  $T_a$ , QRS, T, and U should be used to represent those deflections or groups of deflections to which they were originally assigned, both when the electrocardiogram is normal and when it is abnormal.

"2. In the majority of cases the QRS complex is superimposed upon the  $T_a$  deflection. For this reason the level of reference from which the voltage of the QRS deflections is measured should be the level at which the first of these deflections begins. The voltage of an upward QRS deflection should be measured by estimating the vertical distance between the upper edge of the trace at the beginning of the QRS interval and the upper edge of the trace at the point where the deflection reaches its maximal elevation. The voltage of a downward deflection should be determined by estimating the vertical distance between the

lower edge of the trace at the beginning of the QRS interval and the lower edge of the trace at that point of the deflection which is farthest from the reference level.

"3. In order to indicate how the QRS complex should be subdivided for the purpose of assigning symbols to the deflections which it displays, we may describe a QRS complex which has three components in the following terms: The first deflection begins at the onset of the QRS interval when the trace first leaves the reference level. From this point the trace rises or falls to a turning point, where the direction of its motion is reversed. It may pass through a second or third turning point before crossing to the opposite side of the reference level.\* At this crossing the first deflection ends and the second begins. The second deflection, necessarily opposite in direction to the first, must display one turning point and may display many; it does not end until the trace crosses the reference level for the second time. The third deflection begins at the second crossing and ends at the RS-T junction. No part of the QRS complex which does not display at least one turning point should be considered a separate deflection. If the RS-T junction is displaced and this junction and the last turning point lie on opposite sides of the reference level, that portion of the trace which lies between the last crossing and the RS-T junction should be considered part of the reflection to which the last turning point belongs.

"The earliest QRS deflection which lies above the reference level should be

labeled R. Any downward deflection which precedes R, so defined, should be labeled Q. The first of any downward deflections which may follow R should be labeled S. The first of any upward deflections which may follow S should be labeled R', and the first of any downward deflections which may follow R' should be labeled S'. If it is necessary to label still later deflections of the QRS group, the symbols R'', S'', etc., should be used in accordance with the same principles. When R is absent, so that the QRS complex consists of a single downward deflection, this deflection should be labeled QS. In statistical studies QS, Q, and S deflections should be considered separately.

"A deflection is 'notched' when it displays more than one turning point on the same side of the reference level. A deflection is 'slurred' when it displays a distinct and local 'thickening' on either limb or at its apex, due to a sudden and pronounced change in the slope of the curve or, in other words, in the rate at which the trace is rising or falling.

"When the form of the QRS complex varies from moment to moment because of the effect of the respiratory movements upon the position of the heart, or for some similar reason, the classification of this complex should be determined by the variety of complex which is most abundant, or, if no type is numerically predominant, by the outline of the complexes which are of intermediate form. Very small QRS complexes (largest deflection less than 5 mm.) which display more than three components or multiple slurring and notching should be classed as 'small and bizarre' or 'vibratory.'

"4. The term RS-T junction should be used to indicate the point or shoulder which marks the end of the QRS complex, *i. e.*, the point where the steep

\* When the trace is descending it crosses the reference level at the instant when its lower margin reaches a position below that which it occupied at the beginning of the QRS interval. When the trace is ascending it crosses the reference level at the instant when its upper margin reaches a position above that which it occupied at the beginning of the QRS interval.

slopes of the QRS deflections are more or less abruptly replaced by the more gradual slopes which precede or comprise the first limb of the T wave. In many electrocardiograms the RS-T junction is followed by a nearly horizontal or gently sloping segment which lies on, above, or below the reference level, and ends with the onset of a much steeper slope that rises or falls to the apex of T. It is agreed that the term RS-T segment is a useful name for this part of the ventricular complex when it exists, even though it is proper to regard it as the earliest part of the T deflection. When there is no point between the RS-T junction and the apex of T at which a sharp change in the slope of the trace occurs, this part of the ventricular complex should be called the first limb of the T wave. When the term RS-T segment is used without reference to some particular electrocardiogram or to some particular class of electrocardiograms, it should be understood to refer merely to that part of the ventricular complex which immediately follows the RS-T junction. The reference level for the measurement of the displacement of the RS-T junction should be the same as the level of reference for the measurement of the QRS deflections. The level of reference for the measurement of the RS-T segment, the T wave, and the U wave should be the isoelectric level when this can be determined; otherwise, it should be the level of the trace at the beginning of the QRS interval. The isoelectric level is the level of the trace at the beginning of the P wave when the P wave occurs in its normal relation to the QRS deflections and is not superimposed on T or U.

"5. The term 'diphasic T waves' should be applied to those final ventricular deflections which present two distinct turning points, one on each side of the level of reference. If the earlier

turning point lies below this level, and the latter above it, the diphasic T wave may be said to be of the minus-plus ( $- +$ ) type. If the reverse is the case, it may be said to be of the plus-minus ( $+ -$ ) type. When the term diphasic is used with reference to other deflections, to the QRS complex, or to the ventricular complex as a whole, it should be used in the same sense.

"6. When applied to the QRS complex, the T deflection, to any other electrocardiographic component, or to RS-T displacement, the term 'concordant' should signify that the largest deflection or displacement is in the same direction in Lead III as in Lead I. Under the same circumstances the term 'discordant' should signify that the largest deflection or displacement in Lead III is opposite in direction to that in Lead I."

### Standardization of Precordial Leads

In 1938 the Committee of the American Heart Association for the Standardization of Precordial Leads and a similar committee representing the Cardiac Society of Great Britain and Ireland made joint recommendations with reference to a single precordial lead for routine use. In a supplementary report (*Am. Heart J.* 15:235 (Feb.) 1938), the American committee recommended that when multiple precordial leads were taken, the precordial electrode be paired either with an electrode on the left leg or with a central terminal connected through equal resistances of 5000 or more ohms to three electrodes, one on the right arm, one on the left arm, and one on the left leg. Six precordial points were recommended as suitable locations for the precordial electrode, namely, the  $C_1$ ,  $C_2$ ,  $C_3$ ,  $C_4$ ,  $C_5$ , and  $C_6$  positions. A great deal of painstaking work, however, remains to determine the best location for the re-

remote electrode, the desirability of taking precordial leads routinely, and the best combination of locations for the precordial electrode.

Further tentative recommendations for the standardization of precordial leads made by the Committee of the American Heart Association for the Standardization of Precordial Leads<sup>5</sup> are as follows:

"The Committee is agreed that a single precordial lead from the region of the cardiac apex, or from any other part of the precordium, is inadequate. When multiple precordial leads are taken, it is found that in the vast majority of cases the extreme right side of the precordium and the extreme left side of the precordium yield QRS complexes of more or less opposite form. Leads from a usually small region lying between those from which complexes of opposite types are obtained customarily yield complexes of intermediate or transitional form, which are often difficult to interpret when curves from points farther to the right and from points farther to the left are not available for comparison. The location and size of the region from which transitional complexes are obtained vary greatly from case to case, and are not entirely constant in one and the same subject. When single precordial leads are taken from the outer border of the apex beat, the exploring electrode is, in actual practice, sometimes placed to the right of the region of transition mentioned and sometimes to the left of it, or within it. In serial observations on the same subject inaccuracy in placing this electrode or an alteration in the size or location of the region in question may be responsible for striking changes in the form of the curve obtained by what is technically the same lead.

"This is only one of the causes for dissatisfaction with routine apical leads. When all cases are considered, regard-

less of whether the standard leads are normal or abnormal, it is perhaps true that a lead from the region of the apex or from the left anterior axillary line at the level of the apex will display abnormalities of the ventricular complex more often than any other single precordial lead. When, however, only those cases in which the limb leads are normal are considered, this is certainly not the case. It is now clear that when the standard limb leads are normal, the precordial leads most likely to yield significantly abnormal curves are those from points lying between the left sternal border and the midclavicular line. Consequently, single apical leads most often fail completely in those cases in which multiple precordial leads have most to offer.

"The Committee believes that three is the least number of precordial leads that can be regarded as satisfactory for general purposes. It suggests that those who wish to reduce the number of such leads to a minimum take leads from the  $C_1$ ,  $C_3$ , and  $C_5$  positions. All are urged to take additional leads whenever possible. A lead from the  $C_2$  or a lead from the  $C_4$  position may show diagnostic abnormalities when equally significant changes fail to occur in other leads. Those who follow our recommendations must remember that inversion of the T deflections in leads from the  $C_1$  position is frequently encountered in normal adult subjects. It is believed that those who have had little experience with multiple precordial leads would gain much worthwhile information by taking a full set of six precordial leads on a few normal subjects and on a series of patients with known cardiac abnormalities of the commoner types.

"It is agreed that the information available does not permit a definite decision on empirical grounds as to the best location for the remote electrode with

which the exploring or precordial electrode is paired. It is recommended that the precordial electrode be paired with an electrode on the right arm, with an electrode on the left leg, or with a central terminal connected through equal resistances of 5000 or more ohms\* to three electrodes: one on the right arm, one on the left arm, and one on the left leg. Some, but not all, members of the Committee who formerly placed the remote electrode on the left leg now prefer to place it on the right arm. It has been observed that when the precordial electrocardiogram is judged by the normal standards at present available, a lead from a given point on the precordium may yield an abnormal curve if the exploring electrode is paired with a left leg electrode (CF lead) even though the curve obtained from the same point by using the right arm electrode as the reference point (CR lead) is within normal limits. The opposite situation may also arise. It has also been observed that in certain cases of cardiac infarction in which diagnostic changes are present in the standard limb leads, CF leads display the most striking, and CL leads (leads from the precordium to a left arm electrode) the least striking changes. These observations cannot, however, be interpreted as indicating that CF leads are always more reliable in the diagnosis of infarction than precordial leads of other kinds. There will be less confusion with reference to the effect of the remote electrode if it is clearly understood that each CR lead is equal to the corresponding CF lead plus standard

Lead II; that each CL lead is equal to the corresponding CF lead plus Lead III, and that each central terminal lead is equal to the corresponding CF lead plus one-third the sum of Leads II and III, and is the algebraic mean of the CR, CL, and CF leads from the same precordial point.

"The Committee does not desire at this time to make any recommendation bearing on the question as to whether precordial leads should be taken routinely or in selected cases only. It believes that precordial leads are most likely to yield information of diagnostic importance under the following circumstances: (1) Whenever myocardial infarction is suspected or must be considered a possibility; (2) whenever myocardial disease is suspected or must be considered a possibility and other methods of examination yield no unequivocal evidence of cardiac disease; (3) whenever it is important to distinguish between right and left ventricular hypertrophy or between right and left bundle branch block and this cannot be satisfactorily done by other means; (4) whenever for any reason a complete cardiac study is indicated."

### **Electrocardiographic Criteria of Left Ventricular Hypertrophy**

The value of the electrocardiogram in the detection of left ventricular hypertrophy has been emphasized by Gubner and Ungerleider<sup>6</sup> in a study of: (1) 460 applicants for insurance with left axis deviation, with blood pressure below 140 systolic and 90 diastolic, and without cardiac impairment; (2) 380 applicants with hypertension with left axis deviation whose blood pressure was always above 140 systolic and 90 diastolic, and (3) 100 subjects with advanced hypertensive heart disease with left axis deviation in whom it was assumed that left ventricular hypertrophy was present. It

\* Recent observations indicate that in the vast majority of cases, if not in all, the omission of these resistances has no appreciable effect upon the form of the precordial curves obtained. Consequently, it may be satisfactory to connect the central terminal directly to the three extremity electrodes without the use of intervening resistances of any kind. Further studies should be made before this method is generally adopted.

was found that left ventricular hypertrophy may be considered to be present when left axis deviation occurs in association with any of the following changes:

1. Increase in amplitude of the QRS complex when the sum of the R wave in Lead I and the S wave in Lead III is more than 25 mm. (2.5 millivolts), or when the height of the R wave in Lead I or the S wave in Lead III individually exceeds 16 mm. (1.6 millivolts).

2. Depression of the ST segment in Lead I, even of as slight a degree as 0.5 mm.

3. Flattening of the T wave below 1 mm. amplitude, or other T wave abnormalities in Lead I.

In a previous study (1941), Daley, Ungerleider, and Gubner called attention to the fact that the prognosis in hypertension is dependent not solely on the level of the blood pressure but on the duration of the hypertension, as evidenced by the degree of cardiac enlargement. By application of the electrocardiographic criteria just mentioned, as well as x-ray evidence of left ventricular hypertrophy and aortic widening, to 100 cases with advanced hypertensive heart disease, 90 per cent presented some evidence of left ventricular hypertrophy or arteriosclerosis of the aorta or coronary vessels (which are constant concomitants of hypertension of long standing). The electrocardiogram was found to be somewhat more sensitive than the teleoroentgenogram in the detection of left ventricular hypertrophy (Table 5). However, though electrocardiographic abnormalities occur relatively more frequently than roentgenologic changes, at times there may be definite evidence of left ventricular enlargement in the roentgenogram while the electrocardiogram is quite normal.

A mortality study of 424 insurance applicants with hypertension, divided into

TABLE 5.

COMPARISON OF ELECTROCARDIOGRAMS AND TELEOROENTGENOGRAMS FOR ONE HUNDRED SUBJECTS WITH ADVANCED HYPERTENSIVE DISEASE.

	<i>Percentage of Subjects</i>
Electrocardiogram:	
Pattern of hypertrophy.....	66
Evidence of myocardial disease.....	11
Total abnormalities.....	77
Teleoroentgenogram:	
Apex outside midclavicular line.....	52
Transverse diameter more than 10 per cent above that predicted.....	41
Cardiothoracic ratio above 50 per cent.....	36

four groups on the basis of electrocardiographic findings, *viz.*, (1) normal electrocardiogram; (2) borderline electrocardiographic changes; (3) pattern of left ventricular hypertrophy, and (4) electrocardiographic changes indicative of myocardial disease with or without a pattern of hypertrophy, revealed a distinct increase in mortality with progression in the electrocardiogram toward an abnormal pattern. In the respective groups, the ratio of actual to expected mortality was 186 per cent, 269 per cent, 344 per cent, and 375 per cent, as compared with the normal ratio of 100 per cent. As the electrocardiogram was normal in only 44 per cent of all subjects with hypertension, routine electrocardiographic examination in cases of hypertension would appear desirable.<sup>7</sup>

In 78 per cent of cases with advanced hypertensive heart disease left axis deviation was present, but this finding alone is of no value, since it occurs in a large percentage of normal subjects. The occurrence of left axis deviation in associa-

tion with hypertrophy has been attributed to clockwise rotation of the heart on its longitudinal axis. The degree of axis deviation does not bear any constant relation to the degree of left ventricular hypertrophy. Its usual occurrence with left ventricular hypertrophy in hypertension is due largely to the fact that the body build of subjects with hypertension is most frequently the obese heavy-set type, in which left axis deviation occurs normally because of transverse position of the heart. In slender subjects with left ventricular hypertrophy, left axis deviation is not so often observed. Right ventricular hypertrophy developing late in the course of hypertensive disease tends to nullify the electrical effects of left ventricular hypertrophy, and may cause left axis deviation to disappear.

High voltage of the QRS complex is the earliest and most frequent electrocardiographic change associated with left ventricular hypertrophy, but in the absence of left axis deviation, it is of no significance. The increased amplitude of the QRS complex in left ventricular hypertrophy may be attributed, most reasonably, directly to an increased mass of left ventricular musculature. Robb and Robb (1942), however, in acute experiments on young animals, concluded that increased voltage, particularly of the R wave in Lead I, may be an immediate consequence of acute left ventricular strain, that is, increased intraventricular pressure with dilatation, rather than hypertrophy.

The changes in the ST segment and the T wave are regarded as due to relative ischemia of the inner layers of the left ventricle, instead of involvement of the superficial bulbospiral muscle as claimed by Robb and Robb (1942). While the portions of the superficial sinospiral and bulbospiral muscles which curve inward to form the papillary mus-

cles are frequently involved, the outer layers of the left ventricular myocardium usually are relatively normal, whereas diffuse involvement is observed regularly in the deeper layers of the left ventricle, particularly the subendocardial region. As observed by Barnes (1940) and Kaplan and Katz (1941), changes in the ST segment and the T wave may evolve prior to or even in the absence of left axis deviation. This is particularly apt to occur in subjects of normal or of slender build, more often in association with left ventricular hypertrophy due to aortic insufficiency, nephritic hypertension, or malignant nephrosclerosis. The depression of the ST segment and T wave negativity in Lead I are accompanied by reciprocal elevation in Lead III. In more advanced stages of left ventricular enlargement, changes occur in the terminal deflection in Lead II similar to, though less in degree than, those in Lead I.

Several factors may contribute to produce a relative inadequacy of coronary blood supply in hypertrophy. As shown by Wearn, the capillary count per square millimeter is relatively decreased in hypertrophy. Furthermore, increased thickness of the hypertrophied muscle cells makes difficult rapid diffusion of oxygen, nutriments, and metabolites. In addition to these factors which tend to cause a relative inadequacy of coronary blood flow, there often is an absolute reduction in coronary flow due to associated coronary artery disease, particularly when hypertension is present. Further evidence that the changes in the ST segment and the T wave are due to a metabolic strain is suggested by the fact that the changes are reversible; they have been observed to diminish or disappear promptly in cases in which marked lowering of blood pressure has attended *sympathectomy* and the administration



of *thiocyanates*, *renal extracts*, and *tyrosinase*.

The particular vulnerability of the subendocardial region of the left ventricle is due to a marked gradient in intramyocardial pressure from the epicardium to the endocardium during contraction (demonstrated by Johnson and Di Palma in 1939). In the deeper layers of the left ventricle, during systole, there is a marked increase in intramyocardial pressure, which exceeds aortic pressure and which obstructs coronary flow in this re-

gion, a latent electrocardiographic pattern of left ventricular hypertrophy may be elicited.

Chronic subendocardial ischemia of long duration leads to irreversible changes. Replacement fibrosis occurs, involving the Purkinje network of the left bundle branch which ramifies in the subendocardial region of the interventricular septum and the left ventricle. Interference with left ventricular excitation caused by diffuse involvement of the conduction system leads to slurring, notch-

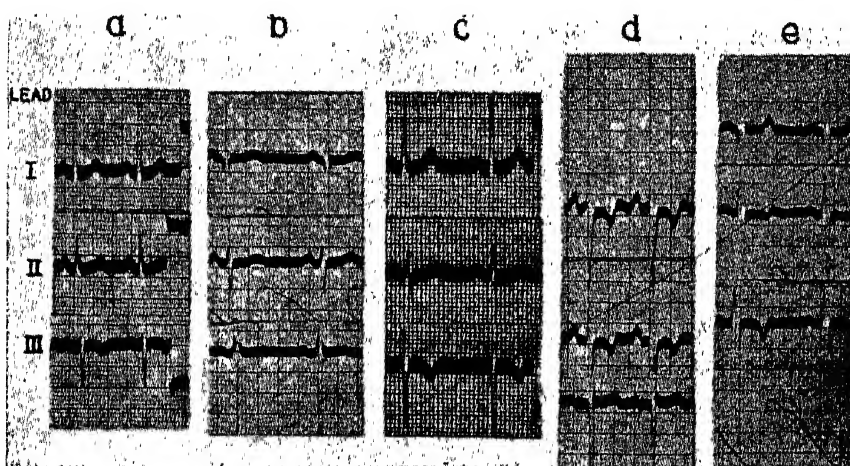


Fig. 1—Left ventricular hypertrophy. Left axis deviation associated with high voltage of QRS complex. (a) A high  $R_1$ , just exceeding normal limits. (b) A deep  $S_3$ . (c) The sum of  $R_1$  and  $S_3$  exceeds 2.5 millivolts. (d) An extremely high  $R_1$ . (e) An extremely deep  $S_3$ .

gion, although there is no interference in coronary flow in the outer zone of the left ventricle or in the right ventricle or auricles, where the intramyocardial pressure does not rise above the arterial pressure. The subendocardial region of the left ventricle and the septum therefore is the area most vulnerable to ischemia; it is the site of predilection of myocardial disease when a relative insufficiency of coronary flow exists, as in hypertrophy, or when there is an absolute decrease in flow, as in coronary artery sclerosis and acute coronary artery occlusion. When a condition such as acute anemia or other strain occurs in a subject with early hy-

pertrophy, and widening of the QRS complex, eventually progressing to the pattern of left bundle branch block, which is frequently encountered in association with long-standing and advanced left ventricular enlargement. The widening of the QRS complex is only in slight part attributable directly to increased thickness of the left ventricular myocardium.

Changes in the ST segment and the T wave in Leads II and III, and ultimately right bundle branch block, occur in conditions associated with chronic right ventricular strain, such as pulmonary stenosis, cor pulmonale, and long-standing mitral disease. The pathogene-

sis of these changes, just as in left ventricular hypertrophy, is related similarly to ischemia of the subendocardial region of the right ventricle consequent to increased intraventricular pressure in the right ventricle.

A terminology suggested by Gubner and Ungerleider for the electrocardio-

graphically exceeds 1.6 millivolts). The high-voltage pattern is illustrated in Fig. 1, p. 221.

**"Left Ventricular Strain"**—This term should be employed when characteristic changes are present in the ST segment and the T wave in the absence of high voltage (Fig. 2) or in the ab-

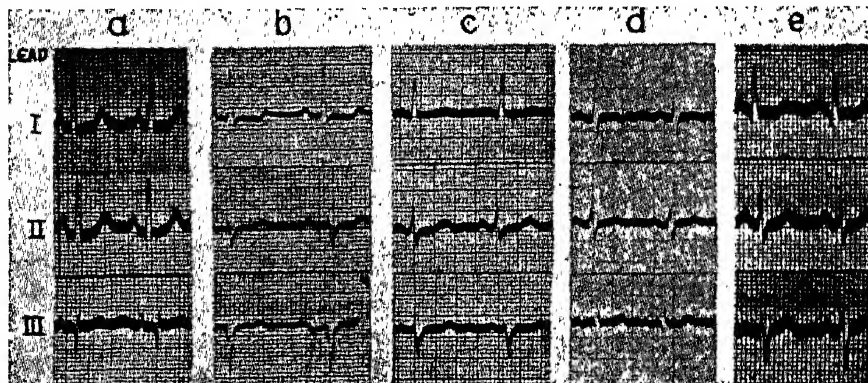


Fig. 2—Left ventricular strain. Left axis deviation associated with changes in the ST segment and the T wave. (a) A slight depression of the ST segment in lead I. (b) A depression of the ST segment in lead I and a reciprocal elevation in lead III. (c) A low  $T_1$ . (d) An inverted  $T_1$ . (e) A depressed ST segment and a diphasic T wave in lead I.

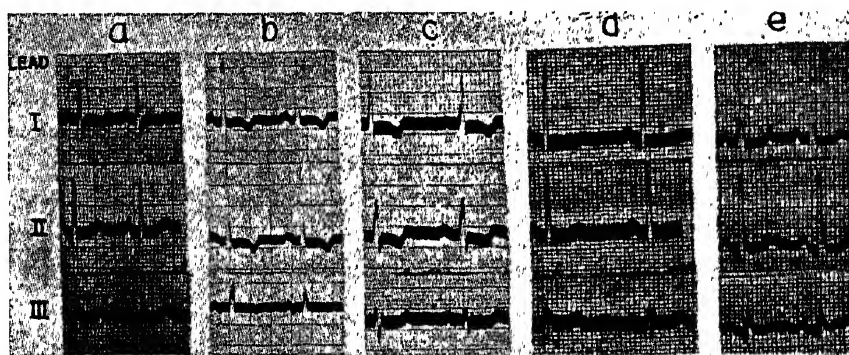


Fig. 3—Left ventricular strain. Changes in the ST segment and the T wave in the absence of left axis deviation. (a) A diphasic  $T_1$ . (b) Inverted  $T_1$  and  $T_2$ . (c) A depressed ST segment and an inverted T wave in lead I and lead II. There is a slight tendency to left axis deviation. (d) A tall R wave, a depressed ST segment and a diphasic T wave in lead I. (e) A tall R wave and a depressed ST segment in lead I.

graphic changes associated with left ventricular hypertrophy is as follows:

**"Left Ventricular Hypertrophy"**—This term may be employed appropriately where left axis deviation is associated with increased amplitude of the QRS complex (the sum of  $R_1$  and  $S_3$  exceeds 2.5 millivolts or  $R_1$  or  $S_3$  indi-

cates the absence of left axis deviation (Fig. 3). The changes in the ST segment and the T wave are less specific of hypertrophy than is high voltage. While characteristic changes in the terminal deflections are usually associated with left ventricular hypertrophy, similar abnormalities may occur in conditions other than hy-

pertrophy when a metabolic strain is placed on the left ventricle (*e. g.*, anemia). Well-marked changes in the ST segment and the T wave may be present in the absence of high voltage of the

graphic changes when both the patterns of hypertrophy (high voltage of the QRS complex) and metabolic strain (changes in the ST segment and T wave) are present (Fig. 4).

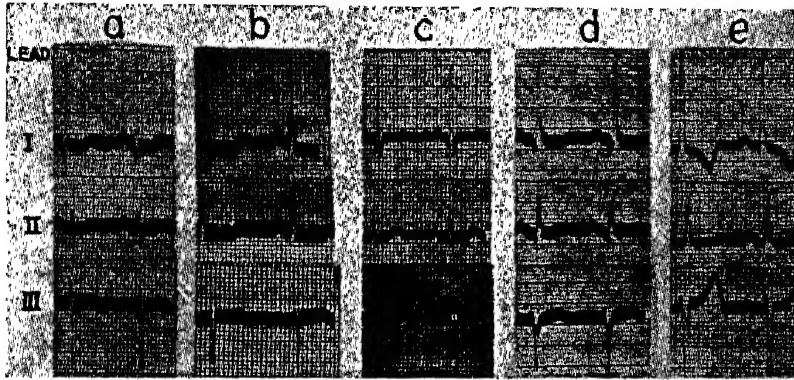


Fig. 4—Left ventricular hypertrophy and strain. (a) A high voltage QRS complex, with the ST segment depressed in lead I and elevated in lead III. (b) A high  $R_1$ , a depressed ST segment in lead I and lead II, and an elevated ST segment in lead III. (c) A high voltage QRS complex, a depressed ST segment, and an inverted T wave in lead I. (e) A typical pattern, with a high voltage QRS complex and characteristic changes in the ST segment and the T wave.

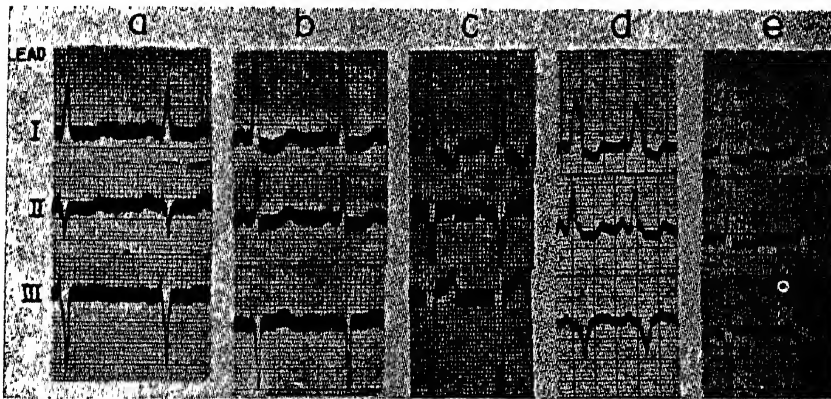


Fig. 5—Left ventricular hypertrophy with myocardial strain and fibrosis. (a) A deep  $S_3$  and a depressed ST segment and a diphasic T wave in lead I. The QRS complex is slurred and notched. (b) A high voltage and depressed ST segment in lead I and lead II.  $R_1$  is notched. (c) Typical changes in voltage and terminal deflection. The QRS complex is widened to twelve hundredths of a second. (d) Left bundle branch block. The QRS complex is notched and widened to thirteen hundredths of a second. (e) Left bundle block with a short PR interval. This is not due to left ventricular hypertrophy but is an anomaly of conduction.

QRS complex, and high voltage of the QRS complex may not infrequently disappear in the later stages of left ventricular hypertrophy with diffuse myocardial disease or after myocardial infarction.

**“Left Ventricular Hypertrophy and Strain”—**This term should be used to connote more advanced electrocardio-

**“Left Ventricular Hypertrophy with Myocardial Strain and Fibrosis (Fig. 5)—**The final stage of left ventricular enlargement as revealed in the electrocardiogram includes, in addition to the aforementioned changes in QRS voltage and terminal deflections, abnormalities in the QRS complex, such as

slurring, notching, and widening, progressing ultimately in its most advanced form to the pattern of left bundle branch block. These abnormalities in the QRS complex are considered to represent diffuse myocardial fibrosis ensuing after long-standing left ventricular strain, which involves the conduction system interfering with the excitation process."

The electrocardiographic patterns described do not always have an exact anatomic counterpart, for the pattern of left bundle branch block occasionally may be produced by localized involvement of the left bundle branch in the interventricular septum without any other left ventricular disease. Also, the pattern of left bundle branch block is encountered in normal persons with a short PR interval, who are subject to attacks of paroxysmal tachycardia (Wolff-Parkinson-White syndrome) (Fig. 5e). The criteria proposed, however indicate the precise electrocardiographic changes which may be considered diagnostic of hypertrophy, and the graded terminology of the more advanced changes further provides an approximate estimate of the degree of left ventricular enlargement, which is more graphic than any single phrase, such as left ventricular preponderance.

### Pulmonary Embolism

In a study of 307 autopsied cases of pulmonary embolism by Currens and Barnes,<sup>8</sup> of which roughly 70 per cent were surgical, 20 per cent medical, and 10 per cent cardiac, the percentage of cases in which the embolism was fatal was considerably less in the medical group (46 per cent) than in the surgical group (74 per cent). Practically all of the cases were 50 or more years of age. In about a third of the cases, not including those with valvular or pericardial disease as causes of cardiac enlargement,

the weight of the heart was more than 400 Gm. This was considered as evidence that there had been hypertension. The size of the heart in the surgical group of cases with pulmonary embolism and in a control surgical group without pulmonary embolism, however, was essentially the same—which fact indicates that hypertension does not predispose to pulmonary embolism among surgical patients.

To determine the relationship between pulmonary embolism and myocardial change which might result from associated coronary artery disease, the hearts of 30 selected cases were subjected to careful anatomic study. Twelve of the 30 cases had presented clinical evidence of more than one pulmonary embolism, 10 had shown evidence of shock for more than two hours before death, and in eight there was moderate to severe coronary sclerosis at necropsy. In 26 instances the embolism was considered as the primary cause of death, and in 4 as only a contributory factor. Sections of heart muscle were examined microscopically for evidence of infarction. Each of the coronary arteries, with its major branches, was cut crosswise at least every 5 mm. and sections were taken from the artery in any region showing significant encroachment on the lumen or evidence of a thrombus. Evidence of acute infarction was found in only five cases, in four of which no significant obstruction was found in the coronary artery, and in the fifth there was fresh coronary thrombosis.

In recent years the rôle that reflex factors may play in the clinical picture of pulmonary embolism has received considerable comment. The occasional patient in whom angina pectoris develops after an attack of pulmonary embolism and who is relieved by *glyceryl trinitrate* does suggest that the coronary

blood flow has been diminished by spasm. However, other factors which affect coronary blood flow in pulmonary embolism are: (a) Fall of arterial pressure, which usually is associated with an increase of heart rate; (b) rise of pressure in the

thebesian veins. Shock also may contribute a great deal to the decrease of coronary blood flow. All these factors combine to impair the function of the right ventricle. The combined effect of increased work of the right ventricle and

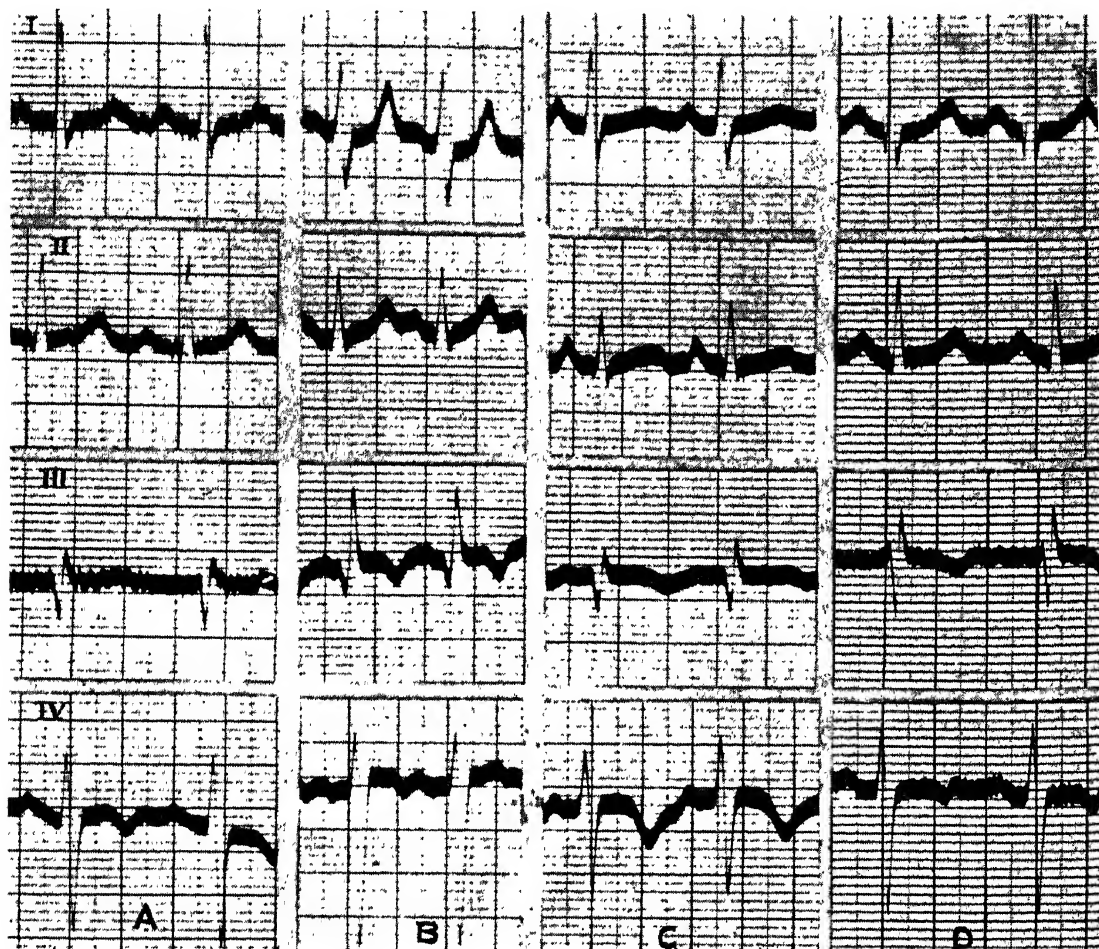


Fig. 6—L. S. A, May 2, 1938, 60 hours after first attack. B, May 18, 1938, 5 hours after attack of dyspnea, collapse, and side pains. C, May 23, 1938, clinically improving. D, April 2, 1941, no attacks since May, 1938.

right auricle which increases the pressure in the coronary sinus and thereby decreases the pressure gradient in the coronary arteries, and (c) increase of pressure in the right ventricle which decreases the coronary flow to this side of the heart, since the major portion of the venous return from the right ventricular wall empties into the right ventricle *via*

decreased coronary blood flow may account for the angina pectoris without the necessity of postulating a pulmonocoronary reflex to account for it.

In general, the dominant factor in the production of the electrocardiographic pattern in pulmonary embolism appears to be the strain placed on the right ventricle. The electrocardiographic picture



is variable; the precordial leads are particularly valuable in diagnosis. If the strain is prolonged, marked dilatation occurs and scattered regions of acute infarction of the right ventricle at times can be demonstrated.

**Electrocardiogram in Pulmonary Embolism**—Ten cases of acute cor pulmonale, without underlying heart disease, have been presented by Murnaghan, McGinn, and White,<sup>9</sup> to corroborate the observations made previously by McGinn and White (1935) that a typical electrocardiographic pattern exists in acute cor pulmonale. The electrocardiogram is characterized by right axis deviation with a prominent S wave in Lead I, a depressed ST segment in Lead II and often in Lead I, a Q wave and an inverted T wave in Lead III, and a diphasic or inverted T wave in Lead IV-F. An upward convexity of the ST segment in Lead III is common, and elevation of the ST take-off in this lead occurs in a few cases (Fig. 6b). Since not every patient with pulmonary embolism develops acute cor pulmonale, the typical electrocardiographic changes do not always appear.

Review of an additional series of 92 cases of pulmonary embolism showed that acute cor pulmonale may occur in varying degrees of severity, and that the electrocardiogram provides a means of evaluating the status of the heart, especially when clinical signs indicative of right-sided heart strain are not obvious. In 69 of the 92 cases co-existent heart disease occurred. Two interesting observations made during this study were: (1) Electrocardiographic changes suggestive of acute cor pulmonale were found after the occurrence of pulmonary embolism when the clinical signs of the condition were not apparent, and (2) symptoms of shock and collapse may

predominate even with small emboli. Electrocardiographic changes considered indicative of acute cor pulmonale were present in 16 of the 29 cases in which symptoms of shock predominated, and in 17 of the 63 cases without signs of shock or collapse. In other words, the electrocardiogram gave indication of some degree of acute cor pulmonale in a little more than one-half of the cases when shock predominated, in slightly less than one-quarter of the group without shock, and in about one-third of the entire series, including those patients who had abnormal electrocardiograms as a result of heart disease.

In evaluating the electrocardiogram of a patient suspected of having acute cor pulmonale, it is important to know how much time elapsed between the onset of the attack and the taking of the electrocardiogram. If the obstruction to the pulmonary circulation is small or is overcome soon after its occurrence, embarrassment of the right ventricle will pass off rather quickly. An electrocardiogram taken within a few hours of the attack may afford the only means of recognizing it. This evidence can be available before roentgenologic signs of pulmonary infarction develop. When the possibility of acute cor pulmonale arises, the use of multiple chest leads is recommended. The T wave is most likely to be inverted when the precordial electrode is over the right ventricle. Lead IV-F sometimes records the electrical potential from the right ventricle and sometimes from the left, more especially if left ventricular hypertrophy exists. When in doubt, chest lead positions II and III should be explored, that is, in the fourth intercostal space just to the left of sternum, and midway between that point and the midclavicular line on the line from point 2 to the cardiac apex. Nor-

mally the T wave is upright in these two precordial leads, but in acute cor pulmonale it is inverted (more definitely than in the routine Lead IV).

An accurate history and a careful appraisal of the physical signs are of major importance in the differential diagnosis of severe acute cor pulmonale and coronary artery occlusion. It is important to recognize the fact that either condition may complicate or set off the other (pulmonary embolism from stasis during convalescence from myocardial infarction, or myocardial infarction in a patient with considerable coronary disease whose coronary circulation is decreased by pulmonary embolism); the two conditions then may affect the electrocardiogram. Sometimes the anoxemia resulting from pulmonary embolism may produce transient changes in the electrocardiogram which may simulate somewhat acute cor pulmonale, without the more persistent changes that occur with actual posterior myocardial infarction.

As the most common cause of pulmonary embolism is thrombosis of the veins of the lower extremities, timely diagnosis and operation on the affected veins should be the physician's goal. Widespread recognition of the varied manifestations of pulmonary embolism and prophylactic leg exercises should lead to a sharp decrease in the incidence of fatal pulmonary emboli, especially among patients confined to bed. Bland thrombosis of the veins, the so-called phlebotrombosis, may baffle the most competent physician, and deliver a lethal embolus to the pulmonary circuit before it is recognized. Venography (with a radio-paque dye, such as diodrast) is of value in revealing venous obstruction, especially in the deep veins of the leg. The appropriate vein then can be ligated and the danger from pulmonary embolism considerably reduced.

### Short P-R Interval and Prolonged QRS Complex

Study by Wood, Wolferth and Geckeler<sup>10</sup> of serial histologic sections of a portion of the auriculoventricular groove of the heart of a young male (aged 16 years) with a short P-R interval and a prolonged QRS complex (Fig. 7), who died in an attack of paroxysmal tachycardia, revealed the presence of three ac-

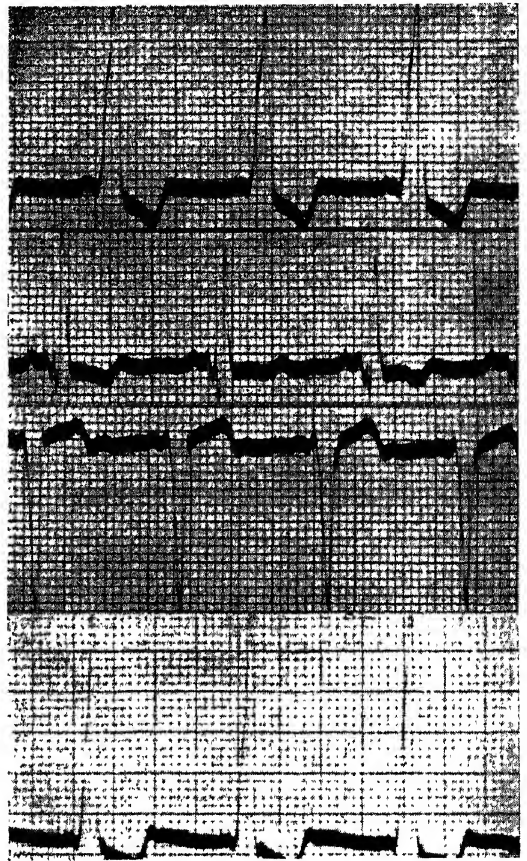


Fig. 7—Electrocardiogram of A. F., taken May 12, 1938, showing the short P-R interval and prolonged QRS complex.

cessory muscular connections at the right lateral border of the heart between the right auricle and right ventricle. During their course two of the muscular connections bridged a small part of the ventricular cavity. Gross examination of the heart showed no evidence of disease.

In making the study, the ventricles were cut off 2 cm. below the auriculo-



ventricular groove and the auricles were cut off 1 cm. above the groove. Blocks of tissue were cut sagittally, beginning just to the right of the aorta. The sectioning was carried around toward the right from that point. A total of 2897 stained sections were studied.

The demonstration of these accessory muscular connections, which should be capable of conducting an impulse from auricle to ventricle, furnishes further support for the hypothesis of an accessory pathway of auriculoventricular conduction as an explanation for the electrocardiographic anomaly of a short P-R interval and a prolonged QRS complex. This hypothesis was first suggested by Holzman and Scherf (1932) and, independently, by Wolferth and Wood (1933). Kent (1913-14) had described an auriculoventricular connection, in the right border of the human heart, connecting the right auricle and ventricle, which he called the "right lateral bundle" and believed might function in certain cases.

## ENDOCARDITIS

**Treatment — Current Results —** A survey by Lichtman<sup>11</sup> of 704 cases of subacute bacterial endocarditis (98 cases due to *Streptococcus viridans*, *Haemophilus influenzae*, and enterococcus from The Mount Sinai Hospital, New York City, and 606 cases obtained from reports in the literature and unpublished communications) has shown the recovery rate with current methods of treatment to average 5.5 per cent. Of 489 cases treated by **sulfonamide** drugs alone, 21 (4.3 per cent) recovered. Of the remaining 215 patients treated by chemotherapy, supplemented by **heparin** or **fever therapy**, 18 (8.4 per cent) recovered; of 109 heparinized patients, 7 (6.4 per cent) recovered; of 61 patients treated with artificial hyperthermia, 4

(6.6 per cent) recovered, and of 45 cases which received combined sulfonamide therapy and **intravenous typhoid vaccine**, 7 (15.5 per cent) recovered.

The evaluation of heparinization as a supplementary measure of treatment requires further trial in properly controlled cases. Artificial fever supplementing sulfonamide therapy produced a slight but significant increase in recovery rate, and intravenous typhoid vaccine appeared also to produce an increased recovery rate subject to further trial. The evaluation of the status of **nearsphenamine** therapy which has been employed in over 70 cases awaits the results of further trial; in one series of 34 cases four recoveries have been reported. The incidence of recovery after surgical ligation of the patent ductus arteriosus in patients with this congenital anomaly with superimposed subacute bacterial endocarditis is well over 50 per cent, as reported by Touroff and his associates, and by Gross. The incidence of spontaneous recovery in subacute bacterial endocarditis is estimated to be approximately 1 per cent.

The recent increase in reported recoveries probably is due to earlier recognition and effective sulfonamide treatment of mild cases. The factors responsible for individual recovery cannot be formulated. Until methods of treatment and results are improved further, every patient with subacute bacterial endocarditis should receive intensive sulfonamide therapy to tolerance. The choice of supplementary therapeutic measures rests at present with individual preference.

Of 67 proved cases of bacterial endocarditis studied by Galbreath and Hull<sup>12</sup> in Charity Hospital, New Orleans, during the years 1938 to 1941, inclusive, 42 of which received sulfonamide therapy, all proved fatal. **Sulfanilamide** alone was administered in 20 cases; **sulfa-**

*nilamide* and *sulfapyridine* in nine cases; *sulfapyridine* alone in six cases; *sulfapyridine* and *sulfathiazole* in three cases; *sulfamethylthiazole* in one case; *sulfanilamide*, *sulfapyridine*, and *sulfathiazole* in two cases, and *sulfapyridine*, *sulfathiazole*, and *sulfadiazine* in one case. As a rule, the dosage per day was large. In most cases sulfonamide therapy was continued until death, or until toxic effects of the drugs necessitated their discontinuance. Frequent blood transfusions were given to most of the patients. In two cases *hyperpyrexia* induced by intravenous injection of typhoid vaccine was used as an adjunct to sulfonamide therapy. This series of cases is unusual in that almost half of them were due to organisms other than the *Streptococcus viridans*.

Recovery of a patient with bacterial endocarditis following intravenous administration of a massive dose of *sulfadiazine* was reported by Dick (1942). The employment of similar therapy in four cases of bacterial endocarditis by Hull, Bayley and Holoubek<sup>13</sup> proved of no avail; death occurred in every instance. All patients showed gross hematuria following the massive initial intravenous dose of 30 or 40 Gm. One patient who was very ill when the treatment was given developed suppression of urine and died of uremia 11 days after a single intravenous injection of 30 Gm. of the drug; autopsy revealed the presence of necrotizing nephrosis involving principally the collecting tubules. Another patient, who was practically moribund when the drug was administered, died 16 hours after a dose of 30 Gm.; no renal lesions attributable to toxic effect of sulfadiazine were present at autopsy.

**Surgical Treatment of Patency of Ductus Arteriosus Complicated by Subacute Bacterial Endocarditis—**

That *ligation or division of the ductus*, if performed before vegetations have spread to the cardiac valves or aorta, is an effective and safe method of treating subacute *Streptococcus viridans* endarteritis involving a patent ductus arteriosus, has been shown by Touroff<sup>14</sup> in a report of 11 patients (eight females and three males) ranging in age from 9 to 63 years. Five of the patients were in the third decade, two in the fourth, and one each in the first, second, sixth, and seventh decades of life. In nine of the 11 patients, infection occurred during or after the third decade. Ten patients received *chemotherapy* prior to operation (either before or after admission to the hospital) without significant effect. In all cases, the characteristic "machinery" murmur of patent ductus arteriosus was present.

In nine cases the operation consisted of ligation of the ductus, and in two, division of the ductus. Nine patients survived the operation; two, early in the series before the present modification of operative technic, died of operative hemorrhage. Of the nine survivors, six recovered from infection without benefit of chemotherapy; the remaining three patients did not recover from infection, despite chemotherapy. Of the six patients who recovered, none presented evidence of preoperative spread of vegetations to the cardiac valves or aorta. They have been followed for periods of three to 29 months, and all are well and have had repeatedly negative blood cultures. The rapidity with which the blood cultures became sterile after operation was startling. Two patients who had circulatory failure prior to operation have become entirely free of this complication. Of the three patients who failed to recover from the infection, two presented evidence of vegetative valvular lesions prior to operation. The third was as-

sumed to have vegetations at the aortic end of the ductus; this conclusion appeared to be substantiated by the occurrence, for the first time, of splenic infarction nine days after operation. One patient died of subacute *Streptococcus viridans* endarteritis approximately eight months after operation; the other two are unimproved 14 and 16 weeks, respectively, after operation.

Subacute *Streptococcus viridans* endarteritis may involve a patent ductus arteriosus at any age. Under conservative therapy, the disease has proved to be almost invariably fatal. The interests of the patient are best served by proceeding with operation as soon as the diagnosis of superimposed infection has been established. This viewpoint is based upon the following observations: (1) The low incidence of recovery with chemotherapy alone; (2) the variable outcome in cases in which chemotherapy is employed for long periods prior to operation, and (3) the high incidence of recovery after operation, when the latter is performed *before* vegetations have spread to the cardiac valves or into the aorta.

In the earlier stages of infection, the inflammatory process involves only the intima of the ductus; subsequently, however, it may involve more and more of the thickness of the wall, and at a still later stage may extend to the adventitia and surrounding tissues. Friability of the ductus (or aneurysm) and adherence to the surrounding structures greatly increase the likelihood of inadvertent tearing of the ductus as the latter is being manipulated during operation. The hemorrhage in such an accident often is difficult to control, and not infrequently fatal.

If operation is performed while the vegetations remain confined to the pulmonary end of the ductus and the pulmo-

nary artery, a cure may be anticipated fairly regularly. On the other hand, if vegetations have spread to the mitral or aortic valves or into the aorta, operation fails to prevent the growth of these new vegetative lesions, and the latter continue to act as foci from which infective material is released into the peripheral circulation. Aortic spread seems to occur chiefly in cases in which the ductus is short. When vegetations are present at the aortic end of the ductus, they may produce no unusual murmurs and may not result in peripheral embolism prior to operation. Spread of vegetations to the pulmonic valve is difficult to recognize prior to operation. Whether or not a patient with right-sided, vegetative valvular lesions can be cured by operation still remains uncertain. Since the mere presence of additional cardiac murmurs is not a reliable indication of the existence or location of new vegetative lesions, chief reliance must be placed upon the occurrence of peripheral embolism in deciding whether or not operation should be performed. If peripheral embolic lesions are unquestionably present, operation appears to be contraindicated. Although operation in doubtful cases may not always result in recovery from infection, it offers the only remaining chance and, therefore, should be undertaken without hesitation.

Aside from incontrovertible evidence of spread of vegetations, as indicated by the occurrence of peripheral embolic lesions, the only absolute contraindication to operation is clear-cut evidence of the presence of associated, major congenital cardiovascular anomalies, for which the patent ductus acts as a compensating lesion. Under the latter circumstances, the current through the ductus flows from the pulmonary artery into the aorta, and the resultant inadequate oxygenation of the blood produces cyanosis and clubbing

of the fingers; and ligation of the ductus usually leads rapidly to circulatory embarrassment and death. But, in the presence of an associated minor cardiovascular anomaly, without cyanosis, it is safe to proceed with operation. It must be remembered, however, that vegetations are prone to develop at sites of associated cardiac anomalies, whether major or minor.

(After the preparation of this article, another patient with patency of the ductus arteriosus, with superimposed *Staphylococcus aureus* infection, was subjected to surgical operation. The total duration of the infection prior to operation was 11 days. *Ligation* of the ductus, followed by *chemotherapy* and the administration of *Meleney's bacteriophage*, proved effective. Thus the series now consists of 12 operative cases, among which there were seven recoveries, three failures, and two operative deaths.)

## HYPERTENSION

### Relation of Vascular Disease to Hypertension

The exact relationship of vascular disease to hypertension is not known. The almost constant presence of arteriolar sclerosis in kidneys of hypertensive patients dying of heart failure or cerebral hemorrhage has led to the belief that increased peripheral resistance to blood flow offered by generalized arteriolar disease, especially of the kidneys, is the cause of hypertension, but other clinicians are of the opinion that arteriolar disease is secondary to hypertension, the cause of which is still unknown. The presence of severe arteriolar damage at the end stage of the disease, as seen in autopsy material, does not necessarily indicate primary arteriolar disease.

The finding of renal arteriolar sclerosis by Moritz and Oldt (1937) in 109

of 100 cases of chronic hypertension and 100 control cases, 97 of which proved to be cases of chronic hypertension, has been looked upon as confirmatory evidence of renal arteriolar sclerosis being a cause of hypertension. But in a recent study of renal biopsies from 100 hypertensive patients in the course of dorso-lumbar splanchnicectomy for relief of hypertension, Castleman and Smithwick<sup>15</sup> found the morphologic evidence of renal vascular disease in more than half of the cases inadequate to be the sole factor in the production of the hypertension. Most of the 100 patients in the series (43 males and 57 females from 18 to 56 years of age) had systolic blood pressures over 200 and diastolic pressures well over 100 mm. of mercury. Sixty per cent had normal renal function as measured by the phenolsulfonphthalein test. All showed retinal vascular changes from mere arteriolar narrowing to edema with elevation of the optic discs.

Most kidneys were found to be of normal size. To observe the cortical surface, the capsule was incised with a scalpel, and with a groove director was gently reflected over an area approximately 3 cm. in diameter. A wedge-shaped specimen 6 to 7 mm. wide and 5 mm. deep was removed with a scalpel. The biopsy wound was sutured with cotton or silk and covered with a small piece of adjacent fat. Twenty-eight per cent of the biopsies showed no or insignificant vascular disease, and an additional 25 per cent only mild changes. Thirty-three patients (22 females and 11 males) showed vascular disease, usually severe in degree, in every vessel, and the remaining 14 patients (10 males and four females) had most severe renal vascular disease, with involvement of every vessel, scarring of many glomeruli and atrophy of surrounding tubules.

The conclusion is drawn that in man there not infrequently exists a state of hypertension in which evidence of renal vascular disease is either absent or is insufficient to explain the elevated blood pressure. In many cases some other functional factor or factors primarily responsible for the hypertensive state apparently precede the appearance of renal vascular disease. Very probably, the vascular disease, once established, aggravates the already present hypertension, which in turn accelerates the arteriosclerosis—a vicious cycle. This is the stage in which the kidney is found post-mortem and on which the theory of the primary vascular origin of essential hypertension is based.

The finding by Blackman (1939) of sclerotic plaques projecting into the lumens of the main renal arteries of 43 (86 per cent) and of marked stenosis of one or both renal arteries of 27 (54 per cent) of 50 cases of essential hypertension—after fixation of the specimens in Kaiserling's solution, mounting, and staining—suggested that chronic hypertension in humans may be the result of renal ischemia, analogous to that produced in animals by the application of a silver clamp to the renal artery (Goldblatt). But recent study by Lisa, Eckstein, and Solomon<sup>16</sup> of the main renal arteries has failed to reveal consistent correlation between the condition or caliber of these vessels and the presence or absence of hypertension, when the caliber of the vessels was measured in the fresh state. Of the 100 cases studied by Lisa and his collaborators, 56 (31 males, 25 females) were hypertensive, and 44 (27 males, 17 females) were nonhypertensive. The average age of the hypertensive group was 63.5 years, and of the nonhypertensive group, 55.6 years. Forty-seven of the 56 hypertensive individuals were over 50 years of age.

The renal arteries were dissected free throughout their entire length and careful measurements of the main vessels and all aberrant branches including the mouths were obtained with graduated sounds. Cross sections of the vessels were made at the narrowest point; when no perceptible narrowing existed, sections were taken 1 cm. from the mouth. The tissues were fixed in formalin, cut, and stained with hematoxylin and eosin and an elastic tissue stain. Marked variations were found in the caliber of non-sclerotic vessels when measured in the fresh state and in the fixed stained preparation; therefore, only the figures obtained in the fresh state were used for analysis.

Among the hypertensive cases, 40 per cent of the vessels were normal (non-sclerotic); among the nonhypertensive cases, the incidence was 56.8 per cent. The average diameter of the normal vessels was 4.1 mm. The average diameter of the vessels in all the cases of hypertension was 4 mm. Although the average diameter of the vessels in the nonhypertensive cases was slightly greater than among the hypertension group, there was no difference when correction was made for the age factor. Very little correlation between the amount of sclerosis and the degree of constriction of the lumen could be demonstrated. Only two instances of extreme stenosis of the renal arteries from sclerotic deposits simulating the Goldblatt dog kidney were found. Linear sclerotic plaques caused practically no narrowing; in many instances severely sclerotic vessels had lumens wider than normal. The degree of cholesterol deposits bore no relationship to the caliber of the vessel. In final analysis, the degree and extent of arteriolar sclerosis estimated from the histologic examination of the kidneys proved a better index of the blood pressure readings

than the caliber of the main renal arteries.

### Hypertension in People Over Forty

The incidence of arterial hypertension in the general population over 40 years of age has become increasingly important because of the greater number of people surviving this age. At the present time,

workers, none in industries exposed to poisons; 2610 residents of homes for aged, and 6502 patients in a general hospital (Mount Sinai, New York City).

As shown on Chart 1, on the basis of the customary limit of hypertension, 150 and/or 90 or over, a little over one-fourth of the men at ages 40-49 have hypertension, a little over two-fifths in

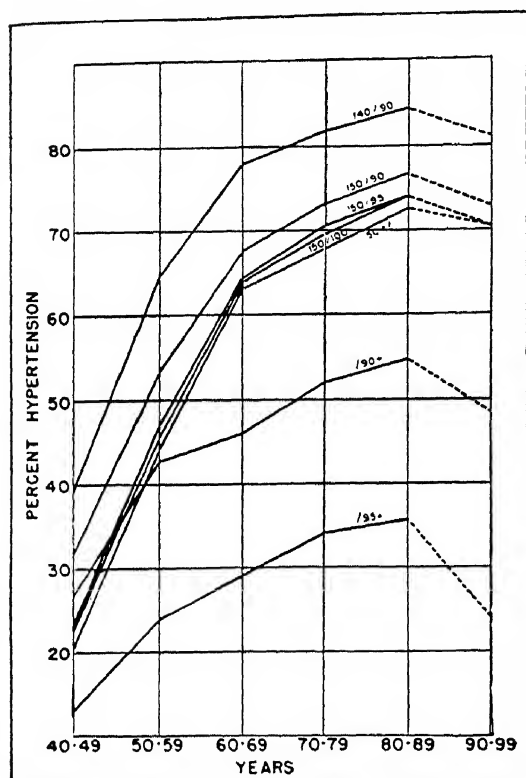


Chart 1—Hypertension in men aged 40-99.

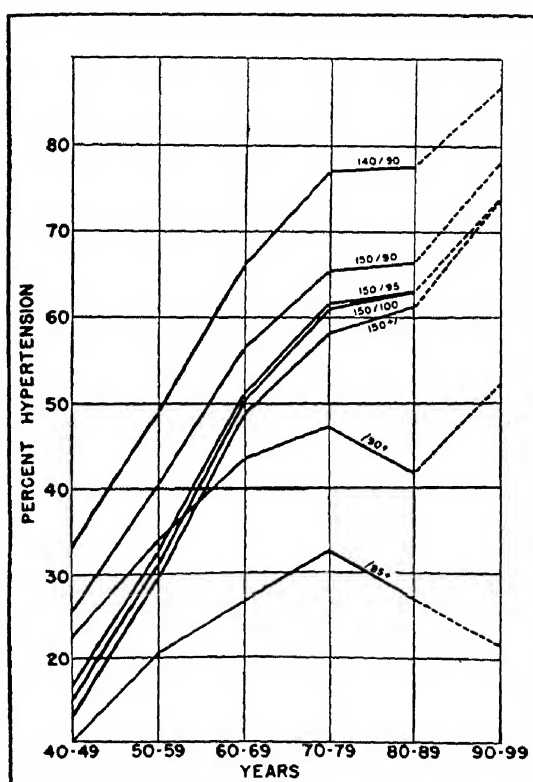


Chart 2—Hypertension in women aged 40-99.

one-third of the population of the United States is 40 years of age or over, and it has been estimated that in 1980 one-half will be. A study by Master, Marks, and Dack<sup>17</sup> of 14,849 persons (8483 males and 6366 females) over 40 years of age, representing a good cross section of the general population in middle and later life, has shown the presence of hypertension at the age of 40 years and over to be "so common that a mild degree and perhaps even a 'moderate' degree can no longer be considered abnormal." The subjects included 5737

the next decade, considerably more than half of those 60-69, nearly two-thirds of those 70-79, and slightly more in the ninth decade. Among women the general contour of the age curve bears a general resemblance to that for males, but the proportions are much higher, there being characteristic differences in the level and the steepness of the curves (SEE: Chart 2). In the first age group 40-49, almost a third have hypertension, more than half in the next decade, more than two-thirds in the seventh decade, and about three-fourths in the eighth

and ninth decades. On the basis of the lowest limit of hypertension, namely 140 and/or 90 or over, about one-third of the men between 40 and 49 years of age have hypertension, and this proportion increases rapidly for the next three decades, until it is over three-fourths in the eighth. Among women, the incidence of hypertension of this degree is approximately 40 per cent between the ages 40 and 49, rising rapidly and exceeding 75 per cent between 60 and 69. The proportions continue to increase, but more slowly, through the ninth decade, when 35 per cent of the women have a blood pressure of 140/90 or over.

Study of the charts reveals that when only diastolic blood pressure is considered, there is a definite lag in the upward slope of the curve of blood pressure with age, beginning at the age of 60, and in men the proportion actually falls after age 80. This emphasizes the well-known fact that the systolic rises more than the diastolic pressure with age, thus causing an increase of pulse pressure. On the basis of these findings, it is estimated that practically one-half of the white male population and 60 per cent of the white female population 40 years of age and over have blood pressure of 140/90 or over, and about one-third of the male population and over two-fifths of the female population at ages 40 and over have blood pressure of 150/100 or over (Table 6).

The high proportion of persons over 40 years of age with hypertension of slight and moderate degree suggests the need of liberalization of the definition of hypertension. From the clinical viewpoint, if at least one-half the persons over 50 years of age have a blood pressure of at least 150/90, it can hardly be said that such a degree of hypertension is abnormal. This point of view

TABLE 6.  
ESTIMATED INCIDENCE OF HYPERTENSION OF VARIOUS DEGREES AMONG WHITE PERSONS IN THE GENERAL POPULATION OVER AGE 40.  
*Based on the incidence in the survey and the age distribution of the population of the United States in 1940.*

Degree of Hypertension,* Mm.	Age Group Years	Percentage	
		Male	Female
140/90 or over	40 and over	49.8	59.8
	50 and over	59.9	72.5
	60 and over	70.5	79.6
	70 and over	77.3	82.2
150/90 or over	40 and over	40.9	50.7
	50 and over	50.3	62.2
	60 and over	59.8	70.2
	70 and over	65.8	74.0
150/100 or over	40 and over	32.5	43.6
	50 and over	43.2	56.5
	60 and over	54.7	66.5
	70 and over	61.8	70.4

\* Cases are included if either the systolic or the diastolic is within the specified limits.

does not in any way conflict with the fact that pressures below this level are more favorable for longevity. "It may well be that these higher pressures are a general and early indication of cardiovascular degeneration. But, of themselves, such pressures cannot be looked on as pathologic. Group longevity is not the sole criterion. Experience shows that in many persons hypertension is not incompatible with a high degree of mental and physical efficiency over long periods of time."

An analysis by Russek<sup>18</sup> of the blood pressure levels of 1000 male subjects, all retired seamen between the ages of 60 and 95 years, also has shown an appreciable increase of the average systolic pressure and pulse pressure with age, and little variation of the average diastolic pressure after the age of 65 years



TABLE 7.  
AVERAGE BLOOD PRESSURE IN OLD AGE.

Age (Years)	Number	Systolic	Diastolic	Pulse Pressure
60-64	120	147	82	65
65-69	201	153	86	67
70-74	157	154	85	69
75-79	248	156	86	70
80-84	170	157	85	72
85-95	104	160	86	74

(Table 7). The mariners were residents of Sailors Snug Harbor, an institution for seafaring men who lack financial support, are unemployed because of the infirmities of old age, or are incapacitated by disease or injury; the majority were of Scandinavian descent. All blood pressures below 150/95 were classified as *normal*; when the systolic and diastolic levels exceeded 150/95, *diastolic hypertension* was considered present, whereas systolic pressures above 150 mm. with diastolic pressures under 95 mm. were regarded as indicative of *systolic hypertension*.

As shown in Table 8, the percentage of "normals" decreased from 67 per cent in the 60-64 year old group to 34 per cent in the 85-95 year group. Of the

1000 subjects, slightly less than half had blood pressures of 150/95 or less. The incidence of systolic hypertension rose progressively with age from 17 per cent to 38 per cent, and, of the entire group, more than one-quarter had this type of blood pressure elevation. On the other hand, the incidence of diastolic hypertension rose more slowly with age (16 per cent to 28 per cent), and those who manifested it comprised less than one-quarter of the entire group. Of the 1000 subjects, therefore, it can be said that approximately two in four were "normals," one in four had "systolic hypertension," and one in four had "diastolic hypertension." Systolic hypertension was present in more than one-third of all subjects over the age of 75 years.

Analysis of the variations in "normal" blood pressure with age (Table 9) revealed that in the 496 subjects in this class the average normal systolic pressure rose from 132 mm. in the 60-69 year old group to 136 mm. in the 80-95 year old group. In sharp contrast to the increase in systolic pressure, the average normal diastolic pressure decreased slightly with age, and the incidence of low diastolic pressures increased concomitantly.

TABLE 8.  
PERCENTAGE INCIDENCE OF NORMAL AND HIGH BLOOD PRESSURE LEVELS IN THE AGED  
(1000 SUBJECTS).

Age (Years)	60-64 (120)	65-69 (201)	70-74 (157)	75-79 (248)	80-84 (170)	85-95 (104)	60-95 (1000)
Normal (496)	67	54	52	39	40	34	49.6
Systolic Hypertension (276)	17	24	26	36	38	38	27.6
Diastolic Hypertension (228)	16	22	22	25	22	28	22.8

TABLE 9.  
ANALYSIS OF TRENDS IN NORMAL GROUP (496 SUBJECTS).

Age (Years)	Systolic				Diastolic			Pulse Pres- sure
	Average (Mm.)	110 or Less	120 or Less	140-150	Average (Mm.)	70 or Less	90-95	
60-69	132	11%	30%	22%	78.3	35%	11%	54
70-79	134	8%	26%	30%	77.1	44%	12%	57
80-95	136	4%	20%	34%	76.0	48%	12%	60

Although 64 per cent of the entire group had systolic pressures above 140 mm., only 30 per cent had diastolic pressures in excess of 90 mm. In the "normal" group the average diastolic pressure was only 77 mm.; for normals and systolic hypertensives combined (77.2 per cent of the entire group) it was 78 mm., and for all the subjects it was 85 mm. These data support the view that the upper level of normal diastolic pressure has in the past been set too high.

Comparison of the expected mortality with the actual mortality calculated from an analysis of 362 consecutive deaths at Sailors Snug Harbor, classified according to blood pressure levels and age at death, revealed that the life expectancy of the subjects with systolic hypertension is strikingly similar to that of the subjects with normal blood pressure, but the prognosis of diastolic hypertension is very different. Life expectancy in the aged would seem, therefore, to be definitely related to the diastolic blood pressure, rather than to the systolic.

Systolic hypertension in old age is commonly regarded as a result of diminished elasticity of the aorta and its large branches, and is usually associated with marked arteriosclerosis of the vessels. Through loss of distensibility of the vessel wall, the arterial pressure becomes elevated above normal with each ventricular systole. At the same time, dimi-

nution of the elastic recoil of the aorta tends to produce a lowering of the diastolic pressure, with a further increase in the pulse pressure. This effect at times is counterbalanced by widening and elongation of the aorta. In some cases, systolic hypertension actually may represent long-standing diastolic hypertension complicated by sclerosis and rigidity of the aorta. When the heart is enlarged, generally it is impossible to exclude the possibility that diastolic hypertension may have been present previously. But, on the other hand, the frequent association of a small heart and marked arteriosclerosis of the aorta, as well as the much more favorable life expectancy in this group, strongly suggests that systolic hypertension in most instances originates as such, and has its own distinct mechanism. Furthermore, it has been shown that increased rigidity of the arterial system, without an associated decrease in internal diameter, does not impose an added burden upon the heart.

In the light of present knowledge, it is impossible to state accurately at what level physiologic blood pressures merge into pathologic ones. If by normal pressure is meant levels consistently compatible with a long and healthy life, then so-called systolic hypertension in the aged should be included in this category. "Although there is increasing evidence that arteriosclerosis is a disease rather than a degenerative change, it cannot be

denied that the process of aging may leave its mark upon the vessels as well as the hair, skin, skeleton, and other structures of the body. The repeated stretching and recoil of the arterial wall and the inherent tendency for elastic tissue to deteriorate with age may be the factors which underlie systolic hypertension. At any rate, it is far more accurate to regard the latter as 'normal' than to identify it with diastolic hypertension, as insurance statistics inadvertently have done."

It is important to bear in mind that other causes for elevation of the systolic pressure, with normal or low diastolic levels, such as hyperthyroidism, aortic insufficiency, and heart block, are associated with increased mortality rates, and, therefore, their inclusion in a study of the arteriosclerotic type of systolic hypertension would alter greatly the life expectancy figures for this group.

In the opinion of Daley, Ungerleider and Gubner,<sup>7</sup> the best criterion of abnormal blood pressure probably is that level at which mortality experience exceeds the predicted average mortality of the population. The comprehensive study made in 1939 by the Joint Committee of the Association of Life Insurance Medical Directors and Actuarial Society of America demonstrated conclusively that levels of blood pressure above 140 systolic and 90 diastolic are definitely abnormal at any age and that the actual exceeds the expected mortality in rapidly rising ratios for systolic or diastolic values above this level. A finding of interest is that the mortality varies with the level of the blood pressure at lower levels, too; that is, that the life expectancy in subjects with blood pressure below average values is decidedly better than the life expectancy of the average population. These findings suggest that, properly, hypertension should not be de-

fined by departures from the average pressure but that the lowest arterial pressure compatible with normal physiological function is the optimal one. Actually, hypertension merges imperceptibly with "normal" values of the blood pressure and, except for the distinctive changes in the arterioles consequent to extreme elevation of the blood pressure in the malignant phase, hypertension is not a disease entity but merely a condition which places somewhat greater strain on the cardiovascular system than exists in the average person, producing identical but accelerated and accentuated effects.

### Treatment of Hypertension

As stated by Landis,<sup>19</sup> treatment of essential hypertension, although at best symptomatic, offers a great deal to the vast majority of patients. In the apprehensive, tense, hardworking patient, resolution of emotional problems, *reassurance, regular and frequent rest* or vacation periods, mild exercise suited to the cardiac reserve, and the judicious administration of sedatives such as *phenobarbital* or *chloral hydrate* in small doses will usually be helpful symptomatically whether or not the blood pressure itself is greatly lowered. Patients should not be permitted to know the fluctuations of blood pressure. By reiterated instruction they should be encouraged to adopt the "way of life" most apt to insure longevity. An optimistic and understanding attitude on the part of the physician is essential.

Manipulations of *diet* have no lasting effect on hypertension with the exception that in obese patients general restriction of caloric intake, producing a gradual loss of weight, often is accompanied by significant lowering of blood pressure and by improvement of symptoms. Restriction of salt intake is indicated only when the edema of cardiac failure ap-

pears. In some patients headache may be relieved by sleeping with the head of the bed slightly elevated, or by avoiding drinking large volumes of water in brief periods. However, as the concentrating power of the kidneys becomes less, the 24-hour intake of water may have to be greater than normal to permit a compensatory polyuria. Alcohol, coffee, and tobacco can be used in moderation except by those individuals who are sensitive to their effects.

Vasodilating drugs, such as *nitroglycerin*, *amyl nitrite*, *sodium nitrite*, and *theophylline*, are useful only during hypertensive paroxysms and even then should be reserved for specific indications or to reduce the blood pressure from a sudden dangerous elevation. In some patients relaxation may be secured by warm baths or massage. *Estrogenic preparations* are worthy of trial in the hypertension of women coinciding with the climacteric. *Bismuth subnitrate*, *insulin-free pancreatic extract*, and vegetable substances, such as *cucurbitacin* and *garlic*, have no significant effect.

*Potassium thiocyanate* in a daily dose of 0.3 to 1.0 Gm. (4.5 to 15 gr.), carefully adjusted for each patient to produce a blood level not above 10 mg. per 100 cc., is reasonably safe provided blood levels are determined frequently. In 30 to 40 per cent of patients carefully controlled dosage reduces blood pressure slightly, and relieves headache, insomnia, and the general tenseness so frequently present. Its efficacy is less in severe hypertension and diminishes as organic changes progress. The patient should be cautioned to discontinue the drug immediately if skin eruptions, weakness, lethargy, nausea, or vomiting appear.

The renin and amine theories of the pathogenesis of essential hypertension have each served as the basis of attempts

at specific therapy, but these are still in the purely experimental stage. *Kidney extracts* and a preparation of *tyrosinase* have reduced hypertension in animals and man, but with both agents local tissue reaction and fever are common. Recent reports ascribe their effects to a nonspecific foreign protein reaction. Such reactions in hypertensive patients are unpredictable as to severity and may be quite dangerous. At the present time none of these substances are sufficiently dependable for general commercial distribution.

*Unilateral nephrectomy* has proved of distinct value in carefully selected cases of "renal" hypertension produced by disease of one kidney. *Omentopexy* to the denuded surface of the kidneys has not been effective. In general, *anterior root section* and *supradiaphragmatic splanchnicectomy* are not as advantageous as *combined lumbodorsal splanchnicectomy*. Because so much depends upon the benign or malignant nature of the disease and the stage at which the operation is performed, conclusions as to the effect of operation on longevity, kidney function, and symptoms have been difficult to assess. Physicians generally hesitate to urge operation for patients in the early, almost asymptomatic stages, though greatest effect is obtainable only at that time. Later, when the functional capacity of the kidneys and heart has been reduced, operation is of no avail. In general, patients over 50 years of age are not suitable for operation.

The surgical viewpoint has been summarized by Smithwick (1942) as follows: "When the indications for operation are clearly defined it is to be expected that a high percentage of carefully selected patients will benefit, as judged by persistent and significant lowering of blood pressure levels. Regression of

eyeground changes, decrease in the size of the heart, improvement in the electrocardiogram, improvement of renal function, and relief of symptoms are noted in certain cases, and present additional ways of evaluating the results of surgery. Furthermore, time may show that life expectancy is increased. There can even now be no doubt of such an increase in cases of malignant hypertension and in patients with severe retinitis who have been subjected to adequate surgery before renal and cardiac functions have been seriously impaired. At the present time, surgery appears to offer the greatest hope for these patients."

The mortality from operative treatment by a surgeon experienced in this field is small. It seems likely that *sympathectomy* should be recommended much more often and much earlier than is now the case, even though available evidence indicates that the procedure represents symptomatic rather than etiologic treatment. A closer consultative relationship between physician and surgeon is essential. In the meantime, vigorous search for more specific, direct, and rational therapy should be continued.

In 9 of 12 patients with essential hypertension studied by Bordley, Galdston, and Dandy<sup>20</sup> at Johns Hopkins Hospital for three to seven years following sympathectomy, symptomatic relief occurred shortly after operation. The level of the arterial pressure was lowered for 6 to 18 months in four of the nine patients treated by infradiaphragmatic splanchnicectomy (Adson-Craig) and for 4½ years in one of three patients treated by supradiaphragmatic splanchnicectomy (Peet). The Peet operation was performed at first, but was supplanted by the Adson-Craig procedure because the latter permits exploration of the kidneys and adrenal glands and interruption of a large part of the sympathetic supply of

the thighs and legs in addition to that of the splanchnic area. Ten of the patients were from 18 to 40 years of age and two were 50 years old at the time of operation. The sole criterion for operation was the presence of incapacitating symptoms.

In five patients the relief from symptoms was associated with a lowering of arterial pressure, and in the remaining four it occurred in the absence of change in hemodynamics. In four cases the symptoms returned when the arterial pressure rose to preoperative levels. In two patients abnormal findings in the heart and eyegrounds regressed during the period of lowered arterial pressure and returned after the pressure again rose. In one patient the electrocardiographic axis changed from left to none at all and the heart decreased in size following operation, even though there was no reduction in the level of arterial pressure, and the apparent improvement lasted about two years. In no instance did the responses to the cold pressor and the sodium amytal test change postoperatively. Postural hypotension of six to nine months' duration occurred in four patients following infradiaphragmatic splanchnic resection, and in none following supradiaphragmatic resection. In three instances postural dyspnea accompanied postural hypotension and gradually subsided in a few months before the latter subsided. In none of the patients treated by the infradiaphragmatic operation was there any alteration of sexual function. Return of arterial pressure to preoperative hypertensive levels was not associated with regeneration of the sympathetic nerves supplying the lower extremities which were severed during the Adson-Craig operation.

Of the three patients who did not obtain symptomatic improvement, one had a cerebral vascular accident two months

prior to operation and thereafter was emotionally unstable and hypochondriacal; the second died of a cerebral accident five weeks following operation, and the third died 22 hours after the second stage of an infradiaphragmatic splanchnicectomy.

Study by Foa, Foa, and Peet<sup>21</sup> of the ratio of the thickness of the wall to the diameter of the lumen (WL) of the arterioles in skeletal muscle in a series of 350 consecutive cases of arterial hypertension (165 males and 185 females), subsequently submitted to supradiaphragmatic splanchnicectomy and lower dorsal sympathetic ganglionectomy and followed for nine months to seven years after operation, showed that patients with more severe thickening of the arterial wall had more severe symptoms, poorer therapeutic results and greater mortality. The percentage of patients with high systolic and diastolic blood pressures became higher as the wall/lumen ratio (WL) increased, and, concurrently, the average WL increased as the blood pressure increased. The only exceptions were the patients with a systolic blood pressure of more than 270 mm. Hg., of which there were seven in the group.

In each case, at the time of operation, a biopsy of four different pieces of intercostal muscle was collected, allowed to cool to room temperature, fixed in 10 per cent formalin, and imbedded in paraffin. At least five arterioles were measured for each patient.

The results of the study are in agreement with the hypothesis that the surgical treatment of hypertension gives better results when hypertension is due to spasm of the arterioles or to a mild, reversible degree of hypertrophy of the muscle fibers in the media, and not when severe permanent anatomical lesions have transformed the majority of the arterioles into narrow and rigid tubes. It is

suggested that the study of hypertensive patients should include, whenever possible, determination of the intensity of the vasomotor reactions, measurement of the effective renal blood flow by diodrast clearance, observation of the blood vessels of the eyegrounds, and determination of the wall/lumen ratio of the arterioles in muscle biopsies.

**Sulfocyanate Therapy**—In a study of 241 individuals at the State Prison and the State Hospital for the Insane, Caviness, Umphlet and Royster<sup>22</sup> emphasize the fact that in *sulfocyanate* therapy of hypertension the lower the effective blood sulfocyanate concentration can be kept, the better the results. Normally in the body there appears to be a balance between pressor substances and sulfocyanates. The concentration of sulfocyanates in the blood tends to vary inversely with the blood pressure level. Sulfocyanates are naturally present in the body in a much higher concentration than any other known depressor substance; the concentration is approximately 50,000 times that of nitrites.

The natural concentration of blood sulfocyanates in the 241 persons, to whom the drug had never been administered, ranged from 0.31 to 2.55 mg. per 100 cc. of blood. In the group of individuals with normal blood pressure the concentration averaged 1.2 mg. per 100 cc. of blood. Samples of blood were collected on the second morning after admission to the institution before breakfast and before tobacco was used. All determinations were made with an Evelyn photoelectric colorimeter. Of 136 patients with hypertension who received sulfocyanate treatment for three months, 92 (67.6 per cent) showed good results, that is, a sustained reduction of at least 15 per cent in both systolic and diastolic pressures. A large number of cases showed more than 15 per cent reduction

in pressure, many presenting a normal pressure after a period of months. Because of less vascular sclerosis, less syphilis, earlier diagnosis and treatment, and better coöperation, private cases showed 79 per cent good results and 7 per cent fair results.

In instituting treatment of hypertension each patient should have a thorough study to discover all factors that might influence the clinical picture. Allergy, faulty digestion, hyperthyroidism and other conditions which occasionally may produce or intensify hypertension should be corrected before specific treatment is begun. In the beginning bed rest may be necessary because of vascular crises, threatened myocardial failure, or other complications; otherwise, better results are obtained by avoiding too much bed rest because of the bad psychologic effect on the patient. Early in the treatment, some rest during the day may be indicated. Small doses of mild sedatives are used almost routinely. Overeating should be avoided; the body weight should be kept as nearly normal as possible. After this regimen has been followed until further improvement is not to be expected, sulfocyanate therapy may be begun if the pressure is still too high. The best results with sulfocyanate therapy are obtained in cases with arteriolar spasm—before the development of arteriolar sclerosis and calcification.

In the use of sulfocyanates the chief objective is to furnish a sufficient amount of the drug to balance an unknown amount of pressor substance and to maintain blood pressure at a satisfactory level. This level must depend on the degree of change in the arterioles and capillaries, the cardiac reserve, and pressor substances. Sulfocyanate therapy should not be prescribed for patients without assurance of coöperation. The initial dose of potassium sulfocyanate is 0.324

Gm. (5 gr.) daily, best given after breakfast. There is no tendency for the development of tolerance to its action; but in many cases a cumulative effect occurs. At first determination of the blood sulfocyanate concentration should be made weekly; later, as the patient's response to the drug is better known, tests are made less frequently, and still later at monthly intervals. Many patients do best with a concentration of 2.5 to 3 mg. per 100 cc. of blood which is within or near natural levels found without sulfocyanate therapy; other patients require a concentration of 5 to 8 mg. or more. Twenty milligrams per 100 cc. of blood is usually accepted as a high safe range. The effects of sulfocyanates develop slowly and persist for a considerable time after therapy has been stopped. Frequently it is necessary to reduce the dose. Occasionally, after several weeks' trial, more than 0.324 Gm. (5 gr.) daily is required. With improvement in blood pressure and symptoms, after weeks or months of treatment, dosage may be reduced gradually.

In elderly arteriosclerotic patients particular care must attend sulfocyanate therapy. Blood pressure must be reduced slowly and gradually to avoid untoward symptoms. In myocardial failure sulfocyanates should not be used until myocardial efficiency has been restored by rest in bed and other therapeutic measures. In angina pectoris, associated with hypertension, sulfocyanates can be used with care; a moderate and slow reduction of pressure tends to relieve angina. There is no tendency toward increased nitrogen retention in the blood. The assumption that sulfocyanates improve the circulation in the kidneys, especially in efferent vessels, apparently has some justification. In many cases of syphilis, hemiplegia, and myocardial failure, fair results may be obtained by pro-



longed treatment. Difficulty has been encountered in the treatment of toxemia of pregnancy.

### Psychosomatic Aspects of Hypertension

Careful study of 93 cases of essential hypertension by Weiss,<sup>23</sup> with special emphasis on the cardiovascular-renal system and personality studies with a detailed investigation of the life situation, has indicated that the emotional component apparently is intimately related to the development of hypertension in some patients, to the production of symptoms in many others, and enters into the treatment of nearly all patients with this disorder. All varieties of personality types, including psychoneuroses and character disorders, were discovered. The compulsive type of character was in the majority, but no significant correlation between group and personality type could be established.

Two psychic tendencies seem to stand in close relationship to hypertension: anxiety and rage. Psychoanalytic observations show that rage is chronic and repressed, and that the resulting psychologic conflict produces "tension" that seems related to hypertension. In some patients it is apparently the chief among the multiple factors that enter into the pathogenesis. The relative importance of constitutional and hereditary factors with regard to the interrelated systems of the body is shown in the accompanying diagram (Fig. 8).

Headache, vertigo, constipation, precordial pain, breathlessness of the sighing respiration type, and fatigue often cannot be explained directly on the basis of the hypertension, being out of proportion to the disease. Psychosomatic study of such patients often reveals the presence of conflict in their makeup and an inability to express their aggression

directly; thus, tensions which cannot be adequately expressed in words or actions seek their way out in the circulatory system by means of body language. Most patients with hypertension see a connection between headache and bowel func-

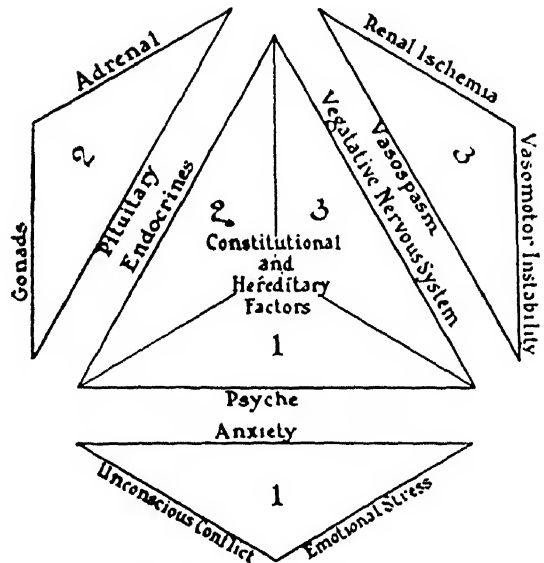


Fig. 8—Diagram to summarize discussion of pathogenesis. The base of the pyramid is made up of constitutional and hereditary factors; the sides consist of interrelated systems which are shown separately as triangles with their sides representing interrelated factors. (Edward Weiss: *Psychosom. Med.*)

tion. When constipation is suffered they are ill, and when the bowel moves freely they are speedily relieved of symptoms. Vertigo frequently is the symbolic representation of insecurity. Fatigue commonly has its origin in emotional conflict, which steals energy which then is not available for useful purposes.

In the past the "organic" understanding of hypertension and the necessity for lowering the blood pressure have been emphasized too much to the exclusion of a more comprehensive and more fundamental understanding of the hypertensive individual. The decreased arterial pressure following sympathectomy and the therapeutic use of thiocyanate do not reverse the process that leads to increased arterial pressure and renal vaso-

constriction. Essential hypertension is a deep-seated constitutional disorder, woven into the very structure and personality of the individual. In many instances it is important to reëducate the patient along the lines of "carrying on" rather than to urge rest.

As stated by Alexander (1937), "Every psychic tendency seeks adequate bodily expression." On this basis, an explanation to the patient that inner tension, which cannot be released through ordinary channels (action or words), may manifest itself in the circulatory system by adding to the problem of hypertension, often leads to a discussion of problems which are of considerable interest and importance from the standpoint of illness. To advise the individual involved in mental conflict not to worry is of little value, especially when no concerted effort is made to find out what is disturbing him. Most of the time the patient does not know just how much he is disturbed nor does he relate the factors actually responsible for his discontent. He is much more apt to project his worries into questions about his blood pressure, heart, brain, and kidneys. Careful inquiry will bring out that his fears are exaggerated and that the reasons he assigns for them are illogical. He should be encouraged to talk about himself as a person rather than as a medical case. Then it will be seen that anxiety bears some relationship to hypertension, and that the unconscious conflict in the personality of the patient can often be treated, resulting in relief of anxiety. If the factor of anxiety is remedied, the patient can become more effective and healthy even if the blood pressure level remains uninfluenced. There is no objection to the effort to lower blood pressure as long as this does not constitute the sole approach to the problem of hypertension.

## PHYSICAL FITNESS

### Resting-Pulse and Blood Pressure Values in Relation to Physical Fitness

That no satisfactory relation exists between basal or sitting pulse rates, sitting systolic or diastolic blood pressure, and physical fitness for strenuous exertion in normal healthy young men, and that emotional factors are largely responsible for the high resting pulse rates that are commonly found during routine medical examination has been shown by Brouha and Heath<sup>24</sup> in a study of 265 college students selected without reference to athletic ability or physical fitness, and a group of college athletes. All the subjects previously had been declared normal after careful medical examination.

As shown in Table 10, under conditions of a routine and strictly private medical examination, performed by a physician known beforehand, six men had a sitting pulse persistently above 100, and 12 of 253 subjects had a systolic blood pressure persistently above 140 mm. The systolic blood pressure remained practically the same whether measured during the medical examination or before an experiment on the treadmill. On the other hand, the sitting pulse rate was definitely higher before the treadmill test than during the medical examination.

The average basal pulse rate of the students was 65, with a range from 45 to 105; the average sitting pulse at the time of the medical examination was 73, with a range from 48 to 105; before the treadmill test, the average sitting pulse increased to 84, with a range from 50 to 124, and 19 subjects had a sitting pulse persistently above 100. In respect to their ability to do hard work, three of the latter were poor, 14 average, and two good. The average sitting pulse of

TABLE 10.

AVERAGES AND EXTREMES OF PULSE AND SYSTOLIC BLOOD PRESSURE IN NORMAL YOUNG MEN AT REST AND BEFORE MUSCULAR EXERCISE.

<i>Measurement</i>	<i>No. of Cases</i>	<i>Average</i>	<i>Ex- tremes</i>	<i>Remarks</i>
<b>Pulse:</b>				
Basal . . . . .	182	65	45-105	0.6% above 100
Recumbent (medical examination)	252	66	40-100	2.8% above 90
Sitting (medical examination) . . .	252	73	48-105	6.3% above 90 and 2.4% above 100
Standing (medical examination) . .	194	82	54-124	12.4% above 100
Sitting (before treadmill walk) . .	127	84	50-124	14.7% above 100
Sitting* (before treadmill run) . . .	231	90	55-136	26.4% above 100, including 6.1% above 110 and 3% above 120
Standing* (before treadmill run) . .	223	123	82-165	6.3% below 100
<b>Systolic blood pressure:</b>				
Recumbent . . . . .	265	115	95-149	1.9% above 140 mm.
Sitting (medical examination) . . .	253	123	100-155	4.7% above 140 mm.
Standing (medical examination) . .	194	121	90-174	7.7% above 140 mm.
Sitting (before treadmill test) . . .	129	123	94-144	3.1% at 140 mm. and 0.8% above 140 mm.

\* These measurements include college athletes.

18 varsity oarsmen before training was 84, with a range from 50 to 116; after training, their average sitting pulse dropped to 67, with a range from 50 to 82. All these men were good or excellent in ability to perform on the treadmill.

With a few exceptions, there was no satisfactory relation between basal or sitting pulse rates and capacity to perform hard work. But a close relation was found between performance capacity and rate of deceleration of the heart after work to exhaustion or to a maximum of 5 minutes on the motor-driven treadmill at 7 miles per hour on an 8.6 per cent grade. Comparison of students with trained oarsmen showed the average pulse of the students one minute after the run to be 156 and of the oarsmen 130, whereas four minutes after the run the pulse was 114 for the students and 96 for the oarsmen. Individual pulses

were regularly higher in the unfit subjects and lower in the fit. The maximum pulse rate of 176 subjects (taken with the Guillemin cardi tachometer) during the run ranged from 167 to 217, with an average of 193 per minute.

A good relation between the pulse at one minute of recovery after the treadmill run and the performance capacity and the fitness index is shown in Fig. 9. The fitness index is derived by dividing the duration of the run in seconds by the sum of three pulse rates counted at convenient intervals during the early recovery. The following interpretation is given to this index in the treadmill test: Below 40, poor physical fitness; from 41 to 75, average; from 76 to 90, good; above 90, excellent.

The average sitting systolic blood pressure for the students was 123 mm., with a range from 102 to 144, and the average for the oarsmen was the same, with a

range from 112 to 136. No satisfactory relation could be found between these measurements and the performance capacity of the students or the oarsmen. No definite relation was established between physical fitness and differences between systolic blood pressure standing and lying, a factor that is a part of the Schneider test.

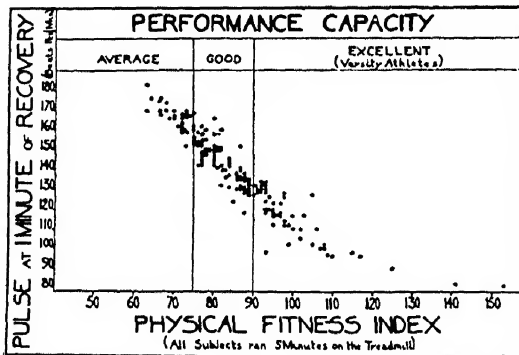


Fig. 9—Pulse after exercise in relation to performance capacity and physical fitness index. It should be noted that the men who were fittest had the lowest pulses in recovery.

The influence of common emotional factors on the heart rate at rest is often underestimated. The average heart rate of 170 subjects recorded by the cardi-tachometer before the beginning of the treadmill run, with the subject standing on the treadmill ready to go but motionless, was 125, with a range from 82 to 165; only eight subjects had a pulse below 100. Four minutes after the treadmill run the average pulse was only 113, with a range from 78 to 150. The same phenomenon was observed both in non-athletic students and well-trained athletes. In the oarsmen the average pulse standing on the treadmill was 120 (extremes 108 to 135), and four minutes after the run it was reduced to 96 (extremes 63 to 108), and in 30 cross-country runners, the average pulse standing on the treadmill was 114 (extremes 96 to 140), and four minutes after the run it was 101 (extremes 80 to 120).

In 61 of 231 subjects resting for 10 minutes before the treadmill run but after a warming up, which consisted in walking at three miles per hour on the treadmill, the lowest sitting pulse rate was above 100 per minute. Fourteen of the latter men were poorly fit, 36 were average, 10 were good, and one was excellent. In comparison, the men who had pulse rates well below 100 under the same conditions had a similar performance capacity. Since no physical work accompanied the increase of pulse rate, the emotional effect of being tested was the responsible factor. This conclusion is further illustrated by the fact that 20 per cent of the subjects had a lower heart rate during the rest period after walking on the treadmill than before walking, and that about 10 per cent of them had a lower sitting pulse five to seven minutes after than immediately before an exhausting run.

On the basis of these findings, it is recommended that when the resting pulse or blood pressure is unusually high the subject should be submitted to a standard amount of strenuous exercise. The estimate of capacity to do hard muscular work should be based on the subject's actual ability to perform it and on the speed of recovery of his heart after exercise, rather than on resting values of pulse and blood pressure alone.

In a discussion of "Cardiac Problems in War Time," White<sup>25</sup> observes that "the normal pulse, at rest or relative rest, even in outstanding athletes, has a tremendous range, actually from 35 to 118 per minute." The pulse rates of six possible winners of a 25-mile marathon run at the starting line immediately before the race began and at the finish line were found to be, respectively, as follows: 64 before and 136 after, 86 and 120, 60 and 140, 62 and 108, 80 and 80, and 118 and 110. The man whose pulse

rate was the fastest at the starting time was the winner of the race in close to record time, and his heart rate actually came down during the gruelling test. The slow heart rate range has been observed in three perfectly normal champions of long distance running, a miler, a two-miler, and a marathoner, and an aviator, whose proved basal heart rates were 37, 38, 35, and 38 per minute, respectively.<sup>25, 26</sup>

## PERIPHERAL VASCULAR DISEASE

### Pulmonary Embolism Due to Quiet Venous Thrombosis

That pulmonary embolism is often caused by quiet thrombosis in the legs is stressed by Homans<sup>27</sup> in a report of 11 ambulatory patients, 10 of whom were treated by peripheral vein division. Embolism due to quiet or silent thrombosis may occur in seemingly well persons. Before any signs of thrombosis appear, it may recur again and again or may prove fatal at a single episode. Embolism from such a thrombosis is more apt to cause repeated pulmonary infarction without fatality than that which complicates operation, accident, or illness. Its symptoms sometimes imitate coronary occlusion, angina pectoris, or pulmonary disease.

Quiet thrombosis, or so-called "phlebotrombosis," is a noninflammatory, reactionless process, which occurs in the deep veins of the legs, usually below the knees. It may occur at any age, but is most commonly seen in the sixth and seventh decades and in obese patients. In its dangerous stage, it causes little venous obstruction. Its peculiar and dangerous quality lies in the tendency to form a loose, soft, detachable thrombus. Thromboses often heal without accident and, occasionally perhaps, without being

noticed. Many develop into an obstructive, outspoken thrombophlebitis. The lack of statistics in regard to the incidence of quiet thrombosis and consequent embolism lies in the fact that the more silent the process, the greater the danger of embolism. A fatal pulmonary accident may arise from a leg that appears quite normal; whereas the great swollen leg of thrombophlebitis almost never causes embolism, since the inflammatory thrombus is fixed by a local reaction in the wall of the vein. A quiet thrombosis should be thought of as consisting of a local process occupying perhaps only a few inches of the vein of the muscles of the calf, but possibly having a loose, soft tail that floats in the popliteal and femoral veins. It is now fairly well established that the great majority of all types of venous thromboses in the legs begin in the calf and foot; in fact, only 10 per cent of all thromboses in the femoral vein are unassociated with deep thrombosis below the knee.

In the presence of quiet venous thrombosis, *operative treatment*, to secure interruption of the thrombosed vein proximal to the source of embolism, always is indicated. Conservative treatment, even if not followed by further embolism, is unlikely to prevent continuance or recurrence of the thrombosis, and the use of *heparin* does not protect against repeated embolism and a fatal outcome. In 10 of the 11 idiopathic cases presented by Homans, division of the femoral, external iliac or common iliac vein was practiced; in the eleventh, operation was not attempted because of suspicion of a cardiac disorder.

In the usual case, when one or more episodes of embolism have occurred and local signs point to thrombosis in one leg, *division of the superficial femoral vein* is sufficient. As this is done, an examination should be made to detect

thrombosis at the level of division. If no thrombus is present below the profunda or at the level of the profunda, division of the superficial femoral is satisfactory. Two possible sources of accident in case of division of the superficial femoral vein in the leg presenting clinical signs of thrombosis are: (a) A separate deep thrombosis in the thigh, already present or to occur later, which may give rise to future embolism; (b) a separate, silent thrombosis in the opposite leg. Not at all rarely an independent thrombosis starts in the deep muscular veins of the thigh, from which it enters the common femoral by way of the great profunda branches. Homans is inclined to believe that in old thrombotic processes attended by embolism, the common femoral vein should always be divided above the profunda or even higher. The femoral vein of the second leg is not explored for a possible separate silent thrombosis when that leg shows no sign of disease and when the evidence for thrombosis in the leg already subjected to operation is good. But if embolism is still occurring when the first leg is already considerably swollen as a result of a process now becoming obstructive in the veins of the groin and pelvis, the place to look for the *present* source of embolism is the second, or innocent-appearing, leg. Under these circumstances venography may prove helpful.

***Division of the common iliac vein*** is the operation of choice in old processes when thrombosis is believed to have occupied, without altogether obstructing, the common femoral vein; in particular, it offers a better collateral venous return than division of the common femoral vein. Division of an iliac vein is not much more difficult to perform than is division of the common femoral, since it can be carried out extraperitoneally, and the higher division gives the patient

and surgeon an assurance of safety, lacking in even a common femoral division, since, almost invariably, the thrombosis has not mounted to the level of operation.

### **Effect of Smoking Cigarettes on Peripheral Blood Flow**

In a study by Evans and Stewart<sup>28</sup> of the effect of smoking cigarettes on the peripheral blood flow of 10 normal male subjects (19 to 36 years of age), by a method with which the average amount of blood allotted to the periphery can be measured in cubic centimeters per square meter per minute, a decrease in blood flow occurred in every instance regardless of the type of cigarette used. Effects on the electrocardiogram, basal metabolic rate, blood pressure, and pulse rate also were recorded. Regular, commercially denicotinized, fully denicotinized, and cigarettes made from cornsilk were used. Measurements were made also when two of the subjects smoked cigarettes through a water pipe.

The greatest percentage decrease in peripheral blood flow took place when the subjects smoked commercially and fully denicotinized cigarettes (Fig. 10). In some instances, the blood flow continued to fall after the subjects stopped smoking, but in all it had begun to return to, or had attained, control levels at the end of 30 minutes after smoking. An increase in blood pressure and pulse rate of essentially the same magnitude and duration resulted from smoking every type of cigarette. In all but five experiments the average skin temperature decreased; the hand temperature fell in every instance except two; the foot temperature always decreased. The decrease in foot temperature was greater than that in hand temperature on all but two occasions. In all experiments except one rapid rises in rectal temperature occurred. This rise in temperature is im-

portant as an index of peripheral vasoconstriction and decreased peripheral blood flow, for the internal temperature represents about 80 per cent of the total body mass.

bed for the same length of time without smoking. The changes in the electrocardiogram, which consisted chiefly of slight lowering of the amplitude of the T waves, were probably of no signifi-

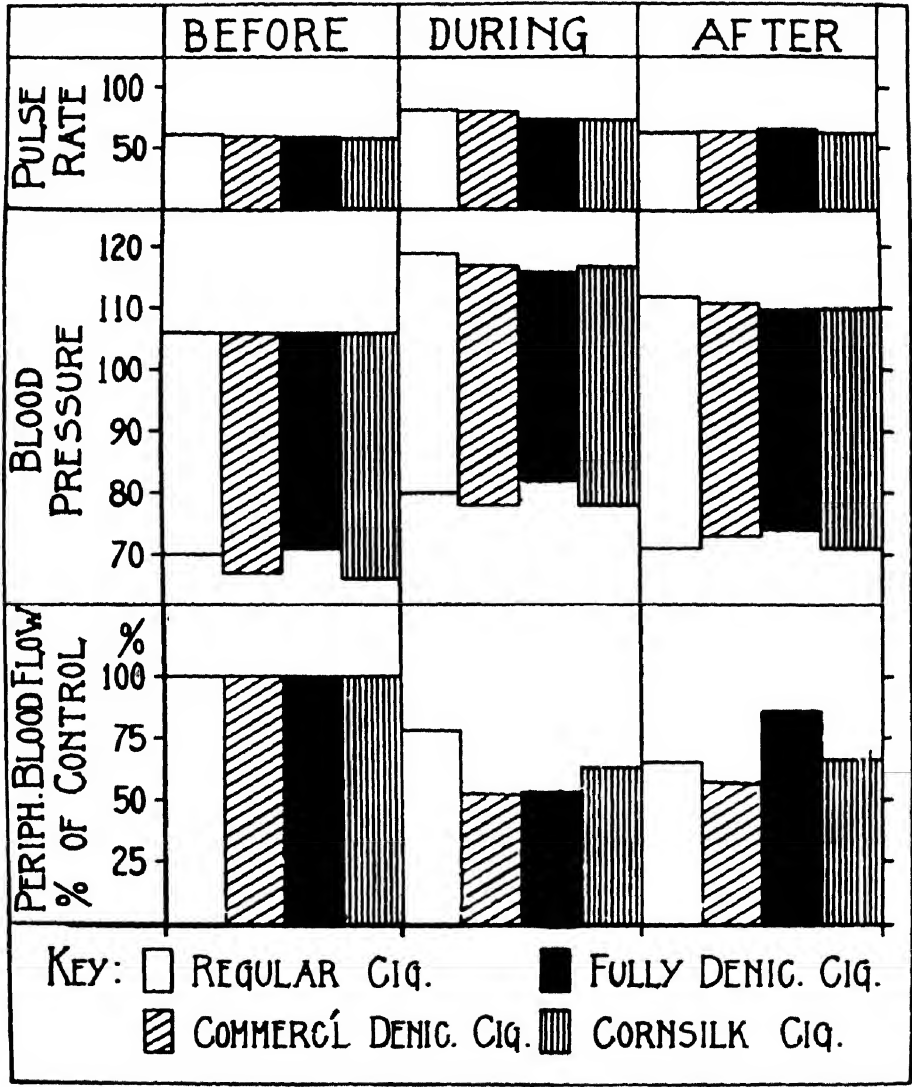


Fig. 10—Changes in average peripheral blood flow as per cent of the control levels, as well as the average blood pressures and average pulse rates of all subjects before, during, and after smoking regular, commercially denicotinized, and fully denicotinized cigarettes, and cigarettes made from cornsilk.

Small increases in basal metabolic rate were observed about twice as often as small decreases, as the result of smoking. The change had no relationship to the kind of cigarette, and was of about the same amount and duration as the changes which occur when normal subjects lie in

cance. An increase in T-wave amplitude, as well as no changes, was also recorded.

In view of the fact that changes occurred after smoking cigarettes which did not contain nicotine as well as after those which did, the effect could not be



attributed to nicotine. Neither could it be attributed to the depth of inspiration or to the inhalation of oxygen or hot air, for the subjects inhaled with normal depth and frequency, and breathing pure oxygen and hot air was found to cause no decrease in peripheral blood flow or rise in blood pressure or pulse rate. It is suggested that sympathetic stimulation brought about by the irritating effect of smoke upon the respiratory tract may be responsible for the changes observed.

From this study it appears that smoking not only regular cigarettes, but also denicotinized cigarettes or cigarettes of any type, should be avoided in the presence of peripheral vascular disease.

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### MISCELLANEOUS

#### Glucose Deficiency as Cause of Cardiovascular Symptoms

The relationship of certain disturbances of cardiovascular function to relative hypoglycemia has been emphasized by Harrison and Finks<sup>29</sup> in a study of 31 cases, observed in the last 204 of their patients with cardiovascular complaints. The most common complaints were nervousness, weakness, palpitation, and pain in the chest. The symptoms practically always occurred two or more hours after meals; at the time of their occurrence the level of the blood sugar usually was either slightly subnormal or within the lower limits of the normal range; they could be relieved by the ingestion of glucose and, in large measure, prevented by dietary regulation, and usually could be reproduced by the injection of insulin. Of the 31 patients, 20 were men. The oldest subject was 65 years of age, the youngest, 26 years; most of them were between the ages of 35 and 55 years.

In six cases the pain in the chest consisted of vague precordial discomfort or

aching; in two, a stabbing sensation, and in one, a feeling of pressure relieved by belching. Thirteen patients experienced a considerable degree of fright and anxiety during the attacks. Dizziness was a prominent feature in nine cases. Eight individuals complained of dyspnea, which usually consisted of repeated sighing and inability to "get a deep breath." In six instances the pain closely resembled that of angina pectoris. Among the less common symptoms were "choking in the throat," arrhythmias, headache, "sinking feeling," blurring of vision, and local paresthesias.

During the attacks the patients usually appeared anxious, the heart beat was forceful, and the heart sounds were loud; the pulse volume was full in most instances, but diminished in others. The pulsations of the aorta usually were pronounced in the suprasternal notch, and the peripheral pulsations were prominent. Tachycardia was the rule, but occasionally bradycardia occurred. The blood pressure varied in either direction; an increase in pulse pressure was the most common change. The skin was sometimes flushed and sometimes pale. The most important associated disorders were hypertension (nine cases), cardiac neurosis (seven cases), hypothyroidism (six cases), arteriosclerotic heart disease (four cases), menopausal syndrome (four cases), paroxysmal tachycardia (three cases), hypertensive encephalopathy, rheumatic heart disease, and hypersensitive carotid sinus (two cases each), and paroxysmal auricular fibrillation (one case).

The circulatory manifestations of relative hypoglycemia are the same as those observed after the administration of insulin. The signs, in general, are similar to those seen in patients with thyrotoxicosis or in normal persons immediately after exercise. They appear to be

related to two mechanisms: Release of epinephrine, and an effect similar to that of anoxia (for fuel deficiency tends to produce in the tissues metabolic disturbances similar to those induced by oxygen deficiency). The increased venous return which results from the release of epinephrine, the dilatation of peripheral vessels as the result of fuel deficiency, or other unknown factors, cause an increase in cardiac output and the typical signs of the "overactive heart."

In 15 of 18 cases in which the response to insulin was studied, some or all of the symptoms which brought the patient to the physician were reproduced by its administration. Ten units of *insulin* were injected three or four hours after a low-protein meal. If at the end of an hour no symptoms appeared, a second injection of 15 units was given. If after an additional 90 minutes no complaints developed, the patient was usually given his meal and the procedure resumed on the following day, employing larger doses. The important point in the test is whether the symptoms produced by insulin are the same as those which occur spontaneously. The response to insulin is of more value in diagnosis than the glucose tolerance test. Both methods of diagnosis are less important than the history.

Observations on persons with symptoms of glucose deficiency, either spontaneous, or induced by insulin, indicate that: (1) Certain individuals may have symptoms of glucose deficiency when the blood sugar is normal; (2) other persons may have extremely low values for blood sugar with minimal symptoms; (3) relief of symptoms may occur with only a slight increase in blood sugar; (4) in a given patient, there is very little parallelism between the level of blood sugar and the severity of symptoms; (5) symptoms of glucose deficiency are more

likely to be related to the rate of decline than to the absolute level of blood sugar, and (6) glucose deficiency, when induced by insulin, is likely to be associated with lower levels of blood sugar than when it occurs spontaneously. It is possible that, in certain patients, and especially those who have symptoms with apparently normal values for blood sugar, the primary disturbance may be in some of the enzymes or hormones which are concerned in the complex processes of transfer, storage, release, and combustion of carbohydrates.

In patients with symptoms due to relative hypoglycemia marked benefit usually can be obtained by a *low-carbohydrate, high-protein* diet. The three regular meals should be relatively small and supplemented by intermediate feedings, total caloric intake sufficient to maintain the weight of thin patients, or adjusted to cause a slow loss of weight in obese patients. High carbohydrate diets with frequent feedings usually have not caused improvement; apparently the marked rise in blood sugar produced by such a regimen leads to excessive insulin production. Diets low in carbohydrate and abundant in fat have been beneficial, but apparently less so than the high-protein diet. As shown by Newburgh and Conn, after a protein meal, the blood sugar curve is relatively stable and free of the postprandial decline which commonly occurs after a carbohydrate meal, because the protein is converted into amino acids which, in turn, are changed into glucose.

### **Fibrosis of Endocardium and Myocardium with Mural Thrombosis**

**Relation to Isolated (Fiedler's) Myocarditis and to Beriberi Heart—**Three cases of heart failure in young adults, not attributable to valvular heart disease, arteriosclerosis or hypertension,

in which the anatomic diagnosis might well have been isolated (Fiedler's) myocarditis, have been reported by Smith and Furth,<sup>30</sup> with the opinion that the changes could have been associated with

phase of illness occupying 12 months; in the other two cases the patients were ill for eight and nine months, respectively. In each there was progressive decline modified slightly by therapeutic

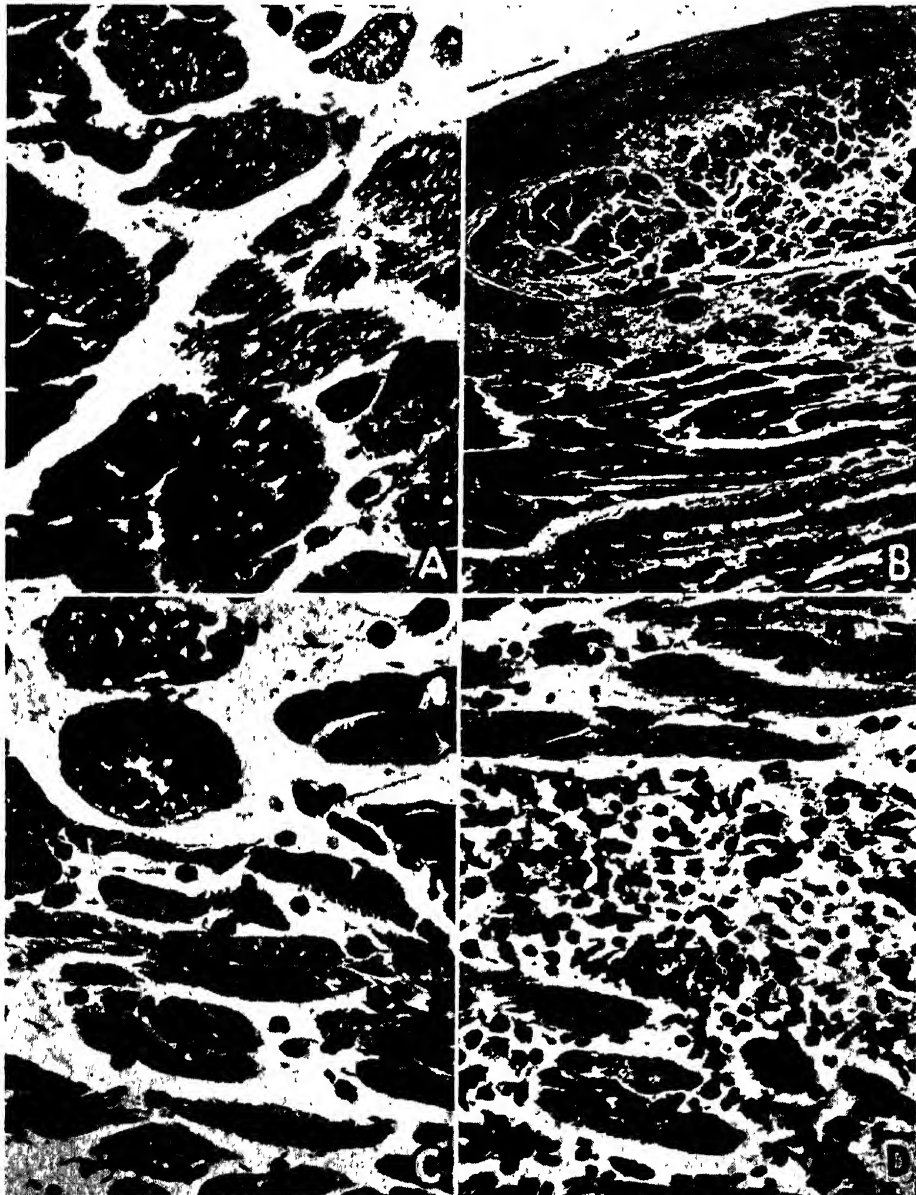


Fig. 11 (Case 1)—Several sections of the myocardium. Part A illustrates the “moth-eaten” appearance of the muscle fibers and the engorgement of the smallest vessels (*venose Stauung of Wenckebach*). Part D illustrates a small focus of cellular infiltration.

deficient diet, representing a variant of beriberi heart. The patients, two men and one woman, were 35 to 40 years of age. In one case symptoms were present during eight years, with the final

measures. One patient, a Chinese man, had lived on a deficient diet over a long period; the other two patients had “poor appetites” and had taken diets probably borderline in their content of vitamin B.

On admission and during hospitalization the symptoms and signs pointed to disease of the cardiovascular system. All patients showed albuminuria, probably related to chronic passive congestion, and the serum protein levels of two patients were 5.9 Gm. and 4.9 Gm. per 100 cc., respectively. Alteration in the form of the T wave and the RT segments of the electrocardiogram in each case pointed to myocardial damage. All patients had received digitalis without significant salutary effects. None made significant response to *thiamine hydrochloride*, nor was diuresis observed when the drug was given intravenously in doses ranging from 20 to 100 mg. over various periods. The course of illness was marked by progressive congestive heart failure with embolic phenomena.

At necropsy each case showed evidence of cardiac failure with chronic passive congestion of the viscera. The hearts were enlarged and dilated, weighing 650, 500, and 460 Gm., respectively. Pulmonary infarction was encountered in two cases, while in the third there were small renal infarcts. Mural thrombi with varying degree of organization were found in both right and left ventricles in two cases, while the left ventricle alone was involved in the third. There was no anatomic evidence of valvular defect, hypertension, arteriosclerosis, or syphilis. Myocardial fibrosis was the conspicuous microscopic change (Fig. 11). The most marked feature in all cases was the widespread endocardial fibrosis in both right and left ventricle, varying from plaque-like deposits to the formation of a dense fibrous tissue plate covering the myocardium and investing the capillary muscles and trabeculae carneae.

Myocardial fibrosis usually has been ascribed to diminution of the myocardial blood supply leading to scattered areas of degeneration and replacement fibrosis.

The findings in these three cases suggest that it also may be the end result of nutritional deficiency. Whether the subendocardial fibers are more susceptible to hydropic degeneration and whether fibrosis supervenes, hydropic degeneration must still be ascertained. As stated by the authors, "it is possible that endocardial and myocardial fibrosis may render the disease process self aggravating and self perpetuating in the nature of a vicious cycle. Muscle degeneration leads to fibrosis and in turn to further degeneration of enclosed muscle fibers, aggravated by rhythmic stretching of the heart, produced or facilitated by some factor not yet recognized. It is conceivable that some myocardial functional change coexists with a nutritional deficiency; for example, the stimulus of diastolic stretching may fail to elicit the usual response leading to hypertrophy when the muscle fibers are injured by hydropic degeneration, but interstitial fibrosis once established may in itself be an aggravating factor."

(Two additional cases, males, aged 54 and 63 years, each with a history of chronic alcoholism, were encountered by the authors after the preparation of this report.)

### Thyrotoxicosis as Sole Cause of Heart Failure

A study by Likoff and Levine<sup>31</sup> of 409 cases of thyrotoxicosis operated upon at the Peter Bent Brigham Hospital from 1923 to 1941, inclusive, of which 331 (81 per cent) were "noncardiacs" and 78 (19 per cent) were "cardiacs," revealed an incidence of 21 cases (6.3 per cent) of definite congestive failure among the "noncardiacs"—showing that thyrotoxicosis not infrequently is the sole cause of congestive heart failure. Among the 78 "cardiacs," of which 45 had hypertensive heart disease, 20 rheumatic

heart disease, 12 coronary artery disease, and one syphilitic aortic insufficiency, there were 39 cases of heart failure (an incidence of 50 per cent).

Congestive heart failure was found to occur more frequently in the female sex, with increasing age, greater duration of the thyrotoxic state, and with the presence of auricular fibrillation. The proportion of females to males among those without heart failure in the "noncardiac" group (310 cases) was  $3\frac{1}{2}$  to 1, while the proportion among those who developed failure was 10 to 1. The patients without other etiologic types of heart disease, presenting congestive failure, were four years older (44 years) than those of the same group without congestive failure (40 years). The duration of thyrotoxicosis in the "noncardiac" group with severe failure was 55 months, with moderate failure 12 months, and with no failure eight months. In the "cardiac" group with failure, the duration of thyrotoxicosis was only ten months. The incidence of auricular fibrillation in the "noncardiac" group without failure was 7 per cent, while with failure it was 38 per cent; the incidence in the "cardiac" group without failure was 15 per cent, and with failure 59 per cent. The arrhythmia, therefore, was four or five times as frequent when heart failure was present than when it was absent.

Thyrotoxicosis *per se* may produce signs and symptoms which closely simulate those found in mitral stenosis. Both disorders may be accompanied by symptoms of cardiac disability; the systolic apical thrill which may be present in thyrotoxicosis may be mistaken for the presystolic thrill of mitral stenosis, because of a rapid rate; the diastolic murmur of mitral stenosis may be absent, and enlargement of the left auricle on roentgenologic examination may be a spe-

cific result of hyperthyroidism. "Masked hyperthyroidism" as a cause of heart failure also is still being overlooked; which error is costly, since the condition is curable.

In 99 cases with cardiac involvement, all but seven of which had a *one-stage subtotal thyroidectomy*, there was no surgical mortality. In 310 cases without heart disease, the surgical mortality was 2.6 per cent. It is not believed, therefore, that the so-called severe thyrocardiac cases require a multiple stage operation. It is felt that they cause less concern than the younger patients with classical Graves' disease when surgical treatment is planned. Among the 60 patients who had heart failure there were no instances of thyroid crisis; whereas, of the remaining 349 without heart failure, 18 developed a thyroid storm.

No satisfactory explanation was found for the heart failure. That increased work of the heart is the only factor involved is difficult to believe. The possibility of a specific or nonspecific toxic factor that injures the myocardium has been suggested. Rare examples of focal myocardial necrosis associated with hyperthyroidism have been reported. Auricular fibrillation, so common in hyperthyroidism, may well be looked upon as a toxic manifestation, for it may precede the elevation in the basal metabolism. Once auricular fibrillation has developed, it can be an added factor in the causation of heart failure, for in an otherwise normal heart prolonged uncontrolled auricular fibrillation may result in heart failure. It is possible that vitamin B deficiency may play a contributory part in the incidence of heart failure. It may be found that patients with hyperthyroidism and heart failure will show more chemical and clinical evidence of vitamin deficiency (especially the B complex) than those without heart failure, and

that those with heart failure had a poorer appetite and a poorer diet than those without failure.

### Aortic Regurgitation Caused by Dilatation of Aortic Orifice and Associated with a Characteristic Valvular Lesion

Aortic regurgitation, which occurs in persons, mostly men, beyond middle age, and is not caused by syphilis, rheumatic

elongation. Depending on the length of the survival period, there is a variable development of structural changes in the aortic leaflets, which apparently is secondary to the dilatation of the aortic ring and is brought about by the eroding action of slow leakage. The change consists of a sclerotic thickening of the midportion of the free margin of the leaflet, without involvement of the commissures. The latter, however, may be slowly



Fig. 12—Various types of central, free marginal sclerosis, enlargement of the sinuses of Valsalva, dilatation of the aortic ring, and widening of the commissures by separation of the leaflets in an aged, hypertensive patient with nonsyphilitic aortic regurgitation. Note irregular thickening and lipping of the endocardium in the midportion of the posterior (middle) leaflet. The posterior sinus is enlarged. The right anterior sinus (R) is ballooned by cotton; the *corpus arantii* of the right leaflet has disappeared; the midportion of the free margin of the leaflet shows crescentic indentation and is indurated; the process is terminated on each side by a bicornuate sclerotic projection (small arrows). The left anterior leaflet shows a small, central, rodlike thickening of the free margin, 0.8 cm. long. The lateral portions of all leaflets are normally delicate, but somewhat elongated. They have been stretched apart, leaving a furrow at the third commissure (X). There is no calcium or atheroma in this aortic valve and scarcely any atheromatosis in the aortic arch.

heart disease, bacterial endocarditis, or arteriosclerotic degeneration, has been discussed by Gouley and Sickel.<sup>32</sup> In most cases dilatation of the aortic ring is present. Occasionally, only supravulvar dilatation of the aortic arch occurs. In all cases the aortic leaflets appear insufficient to meet the need of increased coverage; often they show compensatory

pulled apart in the course of marked ring dilatation. Bicornuate lesions and sclerotic lipping in the midportion of the free margins of the leaflets are characteristic of this type of regurgitation (Fig. 12).

In these cases hypertensive cardiovascular disease usually is present. The valvular insufficiency may be unaccom-



panied by most of the peripheral phenomena which are characteristic of aortic regurgitation of infectious origin. The diastolic murmur is usually merged with an accentuated aortic second sound. Precordial pain is infrequent. Auricular fibrillation is common. Patients with this lesion eventually die of congestive heart failure.

In elderly persons the differential diagnosis is concerned chiefly with the possibility of syphilitic infection. In some cases syphilis may coexist; it may cause aortitis without involving the aortic valvular structure. Occasionally, there may be both ring dilatation ("mechanical" insufficiency) and true syphilitic aortic valvular disease. Serologic reactions are of great importance in diagnosis. Aortic regurgitation in untreated patients more than 50 years of age should not be considered if the blood Wassermann and Kahn reactions are repeatedly negative. The presence of auricular fibrillation in a case of aortic regurgitation in which the serologic reactions are negative almost certainly indicates that the lesion is not syphilitic. When "mechanical" regurgitation is accompanied by positive serologic reactions, the diagnosis, in most instances, will remain a question until necropsy. However, the presence of a loud, snapping aortic second sound, in addition to the diastolic aortic murmur, is suggestive of dilatation of the aortic ring.

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## GASTROENTEROLOGY

RENDALL R. STRAWBRIDGE, M.D.

## STOMACH

## Peptic Ulcer

**Etiology**—Yearly mention has practically always been made of peptic ulcer and gradually during the past few years stress has been placed on the psychosomatic background of this important disease. The present world conflict has most forcefully increased the tendency to regard ulcer as the localized manifestation of a generalized constitutional derangement primarily of psychogenic origin. Winkelstein and Rothschild,<sup>1</sup> by the careful psychiatric examination of 33 young adult males with ulcer, have shown that they all had characteristic psychic backgrounds. They all suffered from chronic frustration and inward direction of repressed, strong emotional stimuli. Yaskin<sup>2</sup> discusses at great length the neuropsychiatric origin of gastrointestinal disturbances. To him the peptic ulcer case has an individual makeup characterized by rigidity, over-conscientiousness, and even intolerance; he is overly honest and meticulous; usually dynamic and even aggressive. Likewise, Wolf's<sup>3</sup> ulcer case histories showed: "prolonged emotional turmoil involving mainly conflict, anxiety, guilt, hostility, and resentment."

**Incidence**—With such a large psychogenic background in the etiology of peptic ulcer it seems natural to expect a rather high incidence of the disease among our armed forces. Thus, Logan and Bransford<sup>4</sup> report that 35 years ago the annual report of the Surgeon General of the Navy listed two admissions to the sick list with peptic ulcer. The last available figures in the report of 1940 (even before we were in actual combat) were 155 peptic ulcers per

100,000 admissions with the greatest number of sick days per case of all gastrointestinal disorders. Palmer<sup>5</sup> has carefully reviewed the British figures and found a great similarity to those obtained in our armed forces. He finds that digestive diseases account for about 15 per cent of all medical patients admitted to military hospitals. Of these 40 to 50 per cent are due to peptic ulcer and of these ulcers the British find 85 per cent are duodenal, whereas the American and Canadian figures are 96 per cent duodenal in contrast to 4 per cent of gastric.

**Disposition of Cases**—The disposition of the soldier with a peptic ulcer has been quite a problem. Up to 1940 only, about 20 per cent were invalided from the U. S. Naval Service, but now the majority of the writers believe they should be discharged to civilian life. Thus, in the beginning of the war, the British sent most of their ulcer cases back to duty but soon found that to be a mistake. Urguhart, observing the Canadian Expeditionary Forces, had the unpleasant experience of readmitting 26 out of 40 cases of ulcer in three months. He, therefore, came to the conclusion early in 1941 that all cases of active duodenal ulcer should be invalided. Similarly, Smellie<sup>6</sup> states in the *Lancet* "whenever the diagnosis of ulcer has been established, the soldier should be invalided and returned to civilian life in the shortest possible time." Allison and Thomas after observing peptic ulcer in the Royal Navy attempt to distinguish between different types. They believe those with recurrent and long periods of pain and those with hemorrhage or perforation, even if recovered,

should be invalidated. On the other hand, those that do well under treatment may be returned to duty with the recommendation for shore service or ships carrying a medical officer. In this country Chamberlin<sup>7</sup> reviewed the figures in the Lawson General Hospital (Army) and found 18 per cent of the medical admissions were to the gastrointestinal section and 31 per cent had proven peptic ulcer. He believes that the man with peptic ulcer is unfit for military service. This author reports a personal communication from the gastrointestinal section at Tilton General Hospital, Fort Dix, N. J., which indicates exactly the same experience. Palmer<sup>5</sup> is more conservative and believes most peptic ulcers should be assigned to limited duty within the continental United States. A much more encouraging report has recently come from the South Pacific zone of combat. Rush<sup>8</sup> reports 200 consecutive patients admitted because of gastrointestinal disorders from March 1942 to March 1943 and found only 19 per cent could actually be diagnosed as peptic ulcer. This figure corresponds, according to Rush, to the findings of the New Zealand forces in the Middle East. Their figure is 18 peptic ulcers per 100 cases of dyspepsia. These figures are about one-half of the number reported in the large continental hospitals by Allison and Chamberlin and the explanation of these differences is not too clear. It would seem that a good many of the cases fortunately broke while they were in training and had been properly managed. From his experiences close to combat areas, Rush believes all peptic ulcer cases should be removed to the interior for rehabilitation and probable mustering out.

**Management**—The actual management of the uncomplicated ulcer patients seems to have changed very little. The

use of frequent feedings of some form of milk or milk substitute with antispasmodics and sedatives at all times and some form of antacid therapy, particularly when indicated, is carefully reviewed by Bockus,<sup>9</sup> Smith and Rivers,<sup>10</sup> Boles<sup>11</sup> and Chaput.<sup>12</sup> All of these authors realize the underlying disturbed involuntary nervous system and stress the importance of avoiding anything that will irritate its highly sensitive sympathetic and parasympathetic branches.

Two articles are of interest in the use of whole milk substitutes. Thus, one author in the past year has recommended the use of potatoes in the dietary treatment of peptic ulcer. Nye<sup>13</sup> believes that the advantages of the potato are: Few people are sensitive to it; it has a high caloric value and a high content of vitamins A, B, and C, as well as minerals; the alkaline reaction of the potato helps to reduce the gastric acidity; and the potato is easily digested. Still another article advises the usage of evaporated milk in the simple uncomplicated ulcer. Here Soper<sup>14</sup> points out that the older frequent whole milk feedings and administration of large doses of alkalies results too often in alkalosis, malnutrition, and even infection with Malta or undulant fever.

In the great majority of cases, the writer believes, the following diet plans taken from the new text by Bockus<sup>9</sup> will be of most value to the average reader in his management of peptic ulcer cases.

#### **Diet Schedules for Patients with Peptic Ulcer** **SCHEDULE A**

**Indications**—This regimen is intended merely as a guide or pattern to be modified according to the needs of the particular case. It may be employed in cases of simple uncomplicated ulcer in patients under 40 years of age, whose occupation is sedentary and who have either moderate distress or symptoms of short duration without evidence of hypersecretion.

**Initial Regimen**—A mixture of  $1\frac{1}{2}$  pints of cold "A" milk,  $\frac{1}{2}$  pint of cold table cream, and 2 rounded tablespoonfuls of lactose is prescribed. This is placed in a quart-sized thermos bottle. Approximately 2 quarts of the mixture will be required each 24 hours. Four ounces of the mixture are taken every hour, on the hour, from 8:00 A. M. until 9:00 P. M. The milk mixture is allowed to stand in a glass before it is taken so that its temperature will approximate that of the room. It should be drunk slowly. The patient should not go to the table to watch others eat. No other food or drink is permissible except water, provided it is not ice cold.

One tablespoonful of plain mineral oil should be taken before retiring in the event of no bowel movement on any given day. If a satisfactory bowel movement does not occur the following morning, a rounded teaspoonful of the following powder should be taken:

**R Extract of**

*belladonna* ..... 0.5 Gm. (8 grains)  
*Heavy magnesia* .. 15.0 Gm. (4 drachms)  
*Precipitated chalk* 15.0 Gm. (4 drachms)  
*Kaolin* ..... 45.0 Gm. ( $1\frac{1}{2}$  ounces)  
*Oil of peppermint* . 2 drops

The thermos bottle mixture should be kept beside the bed at night and a feeding taken if the patient is awakened by pain.

A teaspoonful or more of antispasmodic sedative liquid should be taken when directed:

**R Tincture of**

*belladonna* ..... 30 cc. (1 fluid ounce)  
*Elixir of* ..... q.s. ad 180 cc.  
*phenobarbital* .. (6 fluid ounces)

This mixture is often beneficial during the early days of treatment if nervousness, insomnia, or undue distress is present. It may be taken in the dose of 1 teaspoonful every four hours.

**Follow-up Visit After Four or Five Days**—If symptoms persist, diet "Schedule B" is advised. In the event of continued constipation, substitute prune juice for the first milk feeding and increase the amount of milk sugar in the mixture. It may become necessary that the laxative powder be taken twice daily for a time.

**Follow-up Visit Ten Days After Beginning Treatment**—If satisfactory progress has occurred and symptoms were entirely in abeyance, the following changes may be made: 8:00 A. M., add 4 ounces of strained orange juice with the white of one egg and a teacupful of cream of wheat or farina. 1:00 P. M., add teacupful of jello, gelatin, or junket. 7:00 P. M., add 6 ounces of cream soup, free from condiments

except salt, made from any vegetable except tomato or onion.

**Follow-up Visit Three Weeks After Beginning Treatment**—If the patient continues to be symptom-free, the following changes may be made: 8:00 A. M., add one slice of toasted white bread with jelly or honey. 1:00 P. M., add one soft-cooked egg and a piece of zwieback or two pieces of melba toast with butter. 6:00 P. M., add one slice of toasted white bread with butter and one teacupful of junket, gelatin, jello, custard, or cornstarch. Omit the hourly milk feedings at 9:00 A. M., 2:00 P. M., and 7:00 P. M., *i. e.*, one hour after the three small meals.

**Follow-up Visit Six Weeks After Beginning Treatment**—If all signs indicate satisfactory progress and the patient has been symptom-free continuously, "Bland Six-Meal Diet—Schedule I"—may be prescribed.

**General Directions for the Entire Period of Management**—

1. Excessive physical effort should be avoided while on the strict schedule.
2. Rest periods for at least an hour in the middle of the day and upon returning from work in the evening should be arranged. At least nine hours should be spent in bed at night.
3. Nervous stress and strain should be avoided.
4. Smoking should be discontinued.
5. Pills, laxatives, and other medicines are prohibited without permission from the physician.
6. In the event of a return of symptoms the patient should report at once to the physician. If this is not possible, the hourly feeding schedule should be resumed.

## SCHEDULE B

**Indications**—This is intended as a key or guide to the type of program which may be employed in the treatment of the ulcer patient who is suffering from more than moderate distress, whose attack has been prolonged, or who has had frequent attacks difficult to control, who shows evidence of marked hyperacidity or interdigestive hypersecretion, or both, or who has passed the age of 40 years.

**Initial Regimen**—A mixture of  $1\frac{1}{2}$  pints of cold "A" milk,  $\frac{1}{2}$  pint of cold table cream, and 2 rounded tablespoonfuls of milk sugar is prescribed. This is placed in a quart-sized thermos bottle. Approximately 2 quarts of the mixture will be required each 24 hours. Four ounces of the mixture are taken every hour, on the hour, from 8:00 A. M. to 9:00 P. M. The milk mixture is allowed to stand in a glass for a few minutes before it is taken so that its temperature

will approximate that of the room. The feeding should be drunk slowly. The patient should not go to the table to watch others eat. No other food or drink is permissible except water, that is not cold, which may be taken between feedings.

A tablespoonful of plain mineral oil should be taken before retiring if the bowels have not moved during the day. If a satisfactory movement does not occur the following morning, a rounded teaspoonful of the powder (formula for which is given in "Schedule A") should be taken.

Two liberal teaspoonfuls of colloidal aluminum hydroxide are to be taken every hour 15 minutes before each feeding, beginning at 8:45 A. M. and continuing until 8:45 P. M. Some water may be taken with the gel if desired. The dose is repeated before the patient retires.

A mixture of 10 drops of the tincture of belladonna and 1 teaspoonful of the elixir of phenobarbital in some water is taken 15 minutes before the feedings at 12:00 noon, 4:00 P. M., 8:00 P. M., and before retiring. The amount of belladonna will be increased 2 drops at a time, each day until the mouth becomes dry or the vision is somewhat blurred or the pupils become widely dilated. The amount of the belladonna should then be reduced to that of the previous day and otherwise regulated by the physician. Atropine sulfate, of course, may be substituted for the belladonna, but the dose is somewhat more difficult to regulate.

If night pain has occurred with regularity, 2 or 3 additional teaspoonfuls of the elixir of phenobarbital should be included in the mixture of belladonna and phenobarbital taken before retiring. If night pain has been present and is not controlled by the above regimen after two or three days, have some one awaken the patient one hour previous to the time of the usual occurrence of pain in order that the patient may take a milk feeding and 2 teaspoonfuls of colloidal aluminum hydroxide.

**Follow-up Visit Four Days After Beginning Treatment**—Substitute prune juice for the first milk feeding if the patient is constipated. The amount of milk sugar may be increased for the same reason. If one dose of the laxative powder is ineffectual, two doses may be taken daily. The dose of the milk mixture or the amount of cream in the mixture may be increased if weight gain is desired. No further changes in the diet should be tried at this period in the treatment.

After ten days of freedom from symptoms, 4 ounces of strained orange juice with egg white

may be substituted for the first feeding of prune juice or milk. The dose of aluminum hydroxide may be reduced to 1 teaspoonful.

After three weeks of freedom from symptoms, modifications allowed at the end of ten days in "Schedule A" may be instituted. After four to six weeks of satisfactory progress and freedom from symptoms, modifications allowed at the end of three weeks in "Schedule A" may be started. The aluminum hydroxide may be taken every second hour instead of every hour; possibly the dose of belladonna may be reduced or discontinued at this time. If there is objective evidence of ulcer healing, at the end of an eight- to ten-week period of complete freedom from symptoms, "Schedule I" may be started. During the period of from three to six months, the diet may gradually be increased to approximate that of "Schedule II."

#### **General Directions to the Patient for the Entire Period of Treatment—**

1. Do not eat or drink anything other than the milk mixture. Small amounts of water may be taken when desired between feedings.
2. Avoid physical exertion and nervous excitement and worry as much as possible.
3. Rest for at least an hour in the middle of the day, and for an hour upon returning from work in the evening and get at least nine hours' rest in bed at night.
4. Discontinue smoking.
5. Pills, laxatives, and other medicines are prohibited unless ordered by the physician.
6. In the event of a return of symptoms at any time revert at once to the hourly feeding schedule and report to the physician.

#### **BLAND SIX-MEAL DIET— SCHEDULE I**

This is intended as a key or guide to the type of regimen which may be employed after satisfactory evidence of ulcer healing has occurred (consult Schedules A and B). This schedule may be modified to suit the patient's individual needs.

##### **BREAKFAST**

8:00 A. M.

Fruit: Four ounces of prune juice.

Cereal: Teacupful of cream of wheat, farina, or strained oatmeal. Milk, cream, and sugar as desired.

Bread: One slice of toasted white bread or an equivalent amount of zwieback or melba toast with butter. Plain jelly and honey without wax are permissible.

Beverage: Glass of milk.

1:00 A. M.

Glass of milk and a few plain soda crackers, butter thins, croutons, or melba toast. A broth, devoid of seasoning except salt, made from chicken or lamb and containing barley, rice or noodles, may be substituted for the milk.

#### NOON MEAL

1:00 P. M.

Soup: Bouillon, cupful of broth such as that mentioned at 11:00 A. M. or, preferably, 6 ounces of creamed soup, devoid of condiments except salt, made from any vegetable except tomato or onion.

Bread: Crackers as mentioned at 11:00 A. M. or one slice of toasted white bread. A small serving of cottage cheese, cream cheese, or plain jelly is permissible.

Beverage: Glass of milk.

Dessert: Junket, jello, gelatin, cornstarch, custard, rice pudding, or tapioca pudding.

4:30 P. M.

Glass of milk and crackers of some sort or dry toast, same as 11:00 A. M.

#### EVENING MEAL

5:30 P. M.

Appetizer: Four ounces of the juice of any citrous fruit, or tomato juice, containing the white of an egg.

Main Course: Two soft-cooked eggs or a plain omelet.

Vegetables: One of the following: Baked or mashed white potatoes, plain boiled rice, macaroni or spaghetti without tomato sauce or cheese, mashed carrots. Tender broccoli, cauliflower, or asparagus tips may be substituted for the starchy vegetable if desired. These must be entirely devoid of fiber. Any other green vegetable capable of being pureed to get rid of fiber may be substituted.

Bread: One slice of toasted white bread or an equivalent amount of zwieback or melba toast with butter.

Beverage (if desired): Glass of milk.

Dessert: Baked apple without skin or fiber, applesauce, stewed dried peaches or apricots rid of the skin, prune whip, fruit gelatin, or jello.

9:30 P. M.

Glass of milk. Crackers (if desired), same as 11:00 A. M.

Avoid: Whole grain and dried cereals, cheeses except cottage and cream cheese, hot breads and biscuits, puddings contain-

ing raisins or other roughage, fiber of vegetables or cooked fruits, marmalades and jams, condiments except salt, ice-cold drinks or foods, and all other foods not mentioned in the diet.

Directions: (1) Attempt to have the meals at the same time each day. Do not skip the between-meal feedings. Eat slowly and masticate very thoroughly. Eat sparingly if tired or nervous. Avoid business contacts during the lunch hour. (2) Rest for a half hour after luncheon if possible. Rest for a half hour before the evening meal. Get at least nine hours' rest in bed at night. (3) Do not smoke or use alcohol in any form. (4) If the symptoms return, resume the original diet schedule of hourly feedings and report to your physician at once.

### BLAND SIX-MEAL DIET— SCHEDULE II

This is intended as a key or guide, to be modified for individual requirements, in the follow-up care of ulcer patients who have been free from symptoms and objective evidence of activity of the ulcer for approximately three months. (Consult Schedules A, B and I.)

#### BREAKFAST

8:00 A. M.

Fruit: Small glass of the juice of any fruit which agrees with patient.

Cereal: Any cereal, cooked or dry, except those containing bran. The following are preferable: Cream of wheat, farina, oatmeal, shredded wheat, cornflakes, puffed wheat and puffed rice. Milk, cream, and sugar as desired.

Bread: White bread, toasted or more than 24 hours old, hard rolls of white flour, zwieback, or melba toast. Jelly and honey are permissible.

Beverage: Kaffee-Hag, Sanka coffee, Postum, very weak tea, milk.

11:00 A. M.

Glass of fruit juice, broth, or milk. Crackers if desired.

#### NOON MEAL

1:00 P. M.

Soup: Broth (seasoned only with salt), made from chicken or lamb, containing rice, noodles, or barley; gelatin may be added; creamed soup (seasoned only with salt), made from any vegetable except tomato or onion.

Bread: Same as that allowed at breakfast or soda crackers, butter thins, or other plain crackers devoid of whole meal flour.

Vegetables: One of any of those listed for evening meal.

Main Course: Soft-cooked eggs or plain omelet; sandwiches, made with toasted white bread, of cream cheese, jelly, cream cheese and jelly, or minced chicken.

Beverage: Glass of milk or buttermilk.

Dessert: Jello, gelatin, cornstarch, rice or tapioca pudding, or bread pudding, or any other pudding devoid of raisins or other roughage. Small piece of plain cake, devoid of nuts, cocoanut, or roughage, is permissible.

4: 00 P. M.

Glass of milk or buttermilk with plain crackers.

#### EVENING MEAL

6: 30 P. M.

Appetizer: Any fruit juice which agrees or broth, as for noon meal.

Main Course: Eggs, plain omelet, tender chicken, broiled lamb chops, or one of the following fresh fish: Haddock, halibut, flounder, perch, trout. The fish should be broiled or boiled. Sweetbreads or calf's liver is permissible if very tender.

Vegetables: Baked, mashed, or creamed white potatoes; plain boiled rice; spaghetti or macaroni; mashed or creamed tender carrots; broccoli; asparagus tips; cauliflower. Other green vegetables, such as peas, lima beans, or string beans, may be taken if very young and tender, otherwise they must be pureed. Alligator (avocado) pears or artichokes if free from fiber are permissible.

Dessert: Any of the cooked fruits, such as applesauce, baked apple, stewed dried peaches or apricots, or mush made from berries which have been strained to get rid of the seeds and thickened with cornstarch; banana if thoroughly ripe; plain cake as for luncheon; hard candy is permissible.

9: 30 P. M.

Glass of milk.

Avoid: Tough meat fiber, seafoods except as mentioned above, foods containing nuts, cocoanut and condiments (except salt), meat dressings, meat fillings, gravies, canned or smoked fish, raw fruits except banana, salads and green vegetables (except as mentioned above), alcohol and tobacco.

Directions: (1) Eat slowly and masticate thoroughly. Eat sparingly when tired and nervous. (2) Take the meals at the same time each day. Do not skip the between-meal feedings. (3) Avoid business conversation during the lunch period. Try to rest for at least half an hour after luncheon. Rest for a half hour before the evening meal. Get at least nine hours' rest in bed at night. (4) Revert to your original ulcer schedule following the slightest recurrence of symptoms and report to your physician at once.

### Diaphragmatic (Hiatus) Hernia

Symptoms—Ohler and Ritvo<sup>15</sup> collected from the records of the Boston City Hospital 128 cases of this condition during a period of less than four years and conclude that the condition can no longer be considered rare. The diagnosis should always be included in the differential of anterior chest or upper abdominal complaints or both. The typical symptoms of hiatus hernia were observed by these authors to be a sense of epigastric pain, distress and fulness coming on shortly after or during meals, with frequent difficulty in swallowing solid food. Frequently epigastric pain or distress was more marked at night or when the patient was in the recumbent position and usually the discomfort was relieved when the patient stood upright. There may be substernal pain or dyspnea or both, usually unrelated to exertion and the pain may present radiation similar to that of angina pectoris.

Anemia of a hypochromic type was found to be the rule in these cases, apparently from chronic blood loss arising from the ulceration of the esophageal or gastric mucosa. This frequent hemorrhagic tendency is also pointed out by Sahler and Hampton<sup>16</sup> who reviewed the cases at the Massachusetts General Hospital for a period of ten years. X-ray examination is, of course, the main stay in diagnosis. According to Ohler and

Ritvo, this examination should always begin with fluoroscopic observations without the opaque meal. At this time a careful search should be made for a gas-containing shadow lying at or slightly above the level of the diaphragm. This is of particular importance, since in some cases the hernia reduces itself and disappears on ingestion of the opaque meal. Observations are first made with the patient breathing quietly, then in full inspiration and forced expiration. The frontal and oblique positions are used in the erect, prone, and supine positions. When the opaque meal is administered, the fluoroscopic observations are best begun with the patient in the erect position, but these authors point out that the great majority of these hernias are not demonstrable in such a position and thus many are missed unless studies are made with the patient prone.

From the standpoint of roentgenology Turner<sup>17</sup> reviewed 1500 upper gastrointestinal examinations and found a frequency of 3.5 per cent for the incidence of hiatus hernia. He found the condition least frequent in males and nulliparous females under 30 years of age. He mentions the not too infrequent finding by x-ray of a hiatus hernia without symptoms and describes the type apt to cause symptoms and that which is not apt to. Thus, a broadly dilated esophageal hiatus with a freely mobile and distensible herniating portion of the stomach and normal rugal pattern is least often connected with symptoms. Conversely, a portion of the stomach persistently herniated at the hiatus with no mobility, limited distensibility, and definite prominence of the rugal pattern is most likely to produce symptoms.

**Treatment**—Treatment according to these writers is essentially medical, especially in patients with small lesions and

advanced years. It consists of a *bland, high vitamin diet* of the four or six feeding type with nothing to be taken at bed time. Assumption of the upright position after eating or for a few minutes during the course of the meal is often quite helpful and sleeping at an angle of 45° has often relieved the distressing night symptoms. In their series of cases, Ohler and Ritvo<sup>15</sup> found *alkalis* and *antispasmodic drugs* to be frequently useful. According to them, surgery is indicated only when medical measures fail or reserved for those cases having intractable pain and hemorrhage.

Murphy and Hay<sup>18</sup> similarly reviewed their case histories of patients with hiatal hernia and have recorded data very similar to the former authors. In this series of 72 cases a few additional points are made. They observed the incidence to be much greater in women than men, with a ratio of 6 to 1, and found the average age to be 60 years. Obesity was considered by them to be an important contributory factor as was increased intra-abdominal pressure produced by excess fat in the omentum, a large fibroid or a pregnant uterus. Trauma was also observed to play an etiological rôle in some of the cases. To the medical management as outlined previously, Murphy and Hay suggest that the patient be cautioned against lifting heavy objects or lifting any object from a bending over position. They encouraged the *avoidance of all straining and physical effort* and stress the use of optimal doses of *iron* to handle the hypochromic anemia.

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## THE LIVER

### Cirrhosis of the Liver

**Etiology**—A thorough study of portal cirrhosis has been presented by Ratnoff and Patek.<sup>19</sup> They scrutinized the records of 386 cases from various New



York Hospitals with particular reference to the presence of antecedent factors, signs and symptoms, complications and the prognosis after the development of specific signs. In addition they discuss the causes of death and make a critical review of the pertinent medical literature. In this survey they found no particular evidence of hereditary predisposition, but there was some increased incidence in patients of Italian and Irish stock. Forty to 65 years was the average age and men were affected two to three times as often as women, possibly because of the greater usage of alcohol by men. A dietary deficiency was the rule and alcoholism commonly contributed to the deficient state. Syphilis, exposure to arsenic, malaria, typhoid and paratyphoid fevers, acute hepatitis and thyroid disease appeared to be possible contributory factors in a few of the cases.

**Symptoms**—Flatulent dyspepsia and swelling of the abdomen were the earliest symptoms with loss of weight occurring in about half of the cases and hematemesis in about one-quarter. Ascites, edema, jaundice, a palpable liver or spleen, fever, and evidences of collateral circulation were the chief signs. The appearance of jaundice was observed to be usually a terminal phenomenon. Peripheral neuritis was commonly present and thought by Ratnoff and Patek to be due to nutritional deficiencies.

**Prognosis**—Over two-thirds of the cases were found to end fatally within a year after the onset of jaundice, hematemesis, or ascites. Thirty-five per cent were considered to have died of hepatic failure or cholemia, with hematemesis accounting for the death of one-quarter of the cases and secondary infections for another quarter.

**Management**—The modern management of cirrhosis by *high vitamin, high*

*protein* and *low fat diets* is discussed by Fleming and Snell.<sup>20</sup> Encouraging results were reported.

**Complications**—Ascites, hemorrhage, and hypoproteinemia seem to be the main complications of portal cirrhosis and their individual management deserves special consideration. Ascites can at times be handled by *restricted fluids and a low salt diet* with 8 to 15 grams of *ammonium chloride* daily and *intravenous mercurial injections* two or three times weekly. The next step, if diuretics fail, is *paracentesis abdominis* and, if collateral circulation does not develop, tapplings should be made as needed. To encourage new circulation, *omentopexy* of the Talma or Drummond-Morrison variety has been advised. Cates<sup>21</sup> has reviewed 38 cases on whom omentopexy was performed for the relief of ascites and concludes from a careful follow-up study that the prognosis was no more satisfactory than it would have been if medical treatment alone had been given.

In hemorrhage it is well to use a source of *vitamins C and K* along with the usual routine measures of *rest, nothing by mouth* and *sedation*—preferably other than morphine, for opium derivatives are tolerated very poorly by cirrhotics. At the Mayo Clinic, a technic of injecting the esophageal varices has been established and excellent results are claimed by Snell in the prophylaxis of hemorrhage. The hypoproteinemia of chronic cirrhosis is still under investigation but most means so far advanced for its management have not been too successful. Therefore protein replacement by infusions of *acacia, whole blood, plasma, amino acids* and even *ascitic fluid* so often fail because the badly diseased liver is unable to synthesize properly the required proteins from those so far commercially avail-

able. However, Fagin and Zinn<sup>22</sup> have reported some improvement by the intravenous use of amino acids.

### Diagnostic Aids in Liver Disease

In the past year a new aid in the diagnosis of liver disease has appeared. Yater and Coe<sup>23</sup> have given thorium dioxide sol, known as *thorotrast*, to 286 cases with on apparent immediate or ill effects. They describe in detail their technic which consists of 25 cc. intravenously the first day, on the second day, and again on the third day. On the fourth day x-ray films are made of the abdomen. The drug is engulfed by the reticuloendothelial cells throughout the body and thus the liver and spleen are visualized by the roentgen rays. Interpretation of the films remains as yet somewhat difficult, but the authors are most enthusiastic in their opinion that it is of great value in helping to diagnose: (1) cirrhosis of the liver; (2) the presence of metastases in the liver; and (3) liver abscess. Great stress is likewise placed on the safety of the procedure and more skill in interpretation is to be expected as more cases are reported. Their studies have revealed that there is no evidence of latent radioactivity, depression of hepatic, splenic, or hematopoietic function, lowered resistance to infection, or development of neoplasia at the sight of injection.

Another promising aid in the diagnosis of liver diseases has developed from the report by Gray that the blood serum of patients with hepatic disease is altered in some way so that it flocculates colloidal gold. He found a positive colloidal gold reaction in 93 per cent of cases of hepatic disease in contrast to 2.6 per cent positive reactions in a control group of normal individuals or at least with extrahepatic disease

Sweet, Gray and Allen found that the test was positive in eight or nine cases of definite hepatolenticular degeneration and Bauer, using a slightly different technic, previously had found positive reactions in some cases of hepatic cirrhosis and acute hepatitis, but not in obstructive jaundice. More recently Masteer *et al.*,<sup>24</sup> and Noth and Loew<sup>25</sup> have published data related to a comparison of the colloidal gold reaction with liver function tests now in general use.

These later workers have carefully studied 155 patients with hepatic or biliary tract disease, 90 patients without evident hepatic or biliary tract disease and 25 normal males. In 27 of 30 cases of hepatic cirrhosis the test was positive and in 22 cases of 29 with acute hepatitis a positive reaction was obtained. It was seldom positive in obstructive jaundice and uncomplicated cholecystitis. All the normal males were negative and 14 of 90 cases in which hepatic disease could not be demonstrated by any other examination gave positive reactions. Fifty per cent or more of these 14 cases had syphilis or appreciable elevation in temperature. In the cases of cirrhosis and acute hepatitis, the test usually remained positive after the bromsulphalein and hippuric acid tests had become negative. A negative test was reported in 9 instances in which there were pathologic findings of marked or moderate hepatic damage, and in 6 instances in which slight hepatic pathology was present. By contract it was negative in 4 cases in which pathologic examination revealed a normal liver. These authors conclude that the test is not exceedingly sensitive in many instances, but its persistent positivity in cirrhosis, hepatitis, and certain febrile diseases make it an important one warranting further investigation.

Batty and Gray<sup>26</sup> have applied this test to show that there often is involve-

ment of the liver in diseases of the gallbladder. They studied 100 cases with proved disease of the gallbladder and found positive reactions in 46 per cent when the colloidal gold test was performed. They found the incidence higher in cases with jaundice and lower in those patients who were quiescent with no history of fever or jaundice. They, therefore, conclude that cases with repeated acute attacks, especially with jaundice, should be operated on early before there is evidence of too severe liver damage.

The value of prothrombin response to *vitamin K* as a test of liver function has previously been established, but during the last year several articles have appeared to indicate its value in the separation of intrahepatic and extrahepatic jaundice. Thus a German article has appeared by Armentano and Geher,<sup>27</sup> who observed that in the majority of the cases of obstructive jaundice the prothrombin time was restored to normal within 24 hours after the administration of vitamin K. On the other hand in hepatocellular jaundice, if the prothrombin values are low, normal values may only be obtained after all symptoms of the disease have disappeared. Thus the existence of severe hepatocellular icterus is suggested when prolonged prothrombin times are not restored to normal by one to three vitamin K injections of 30 mg. each. These authors made several other interesting observations. They found that low prothrombin levels were not demonstrated in all of the cases with partial obstruction of the common bile duct and in obstruction by stones associated with cholangitis the prolonged prothrombin time could be restored to normal by *methenamine* injections which resulted in the liberation of vitamin K following the destruction of the colon bacilli. In cases with cardiac decompensation and

an enlarged liver, low prothrombin levels were the rule and they spontaneously increased with the return of compensation. However, according to these authors, failure to restore compensation by the administration of vitamin K may signify the presence of a beginning cirrhosis. Another observation by these men was that prothrombin levels of 20 per cent or less are not always associated with spontaneous hemorrhage. They found the prothrombin time normal in practically all cases of hemorrhagic diathesis.

Allen<sup>28</sup> in this country has come to the same conclusion and makes the statement that "the differential diagnosis between intrahepatic and obstructive jaundice can be made with a high degree of accuracy when one observes the plasma prothrombin response to a course of vitamin K therapy." There is usually a rapid response to vitamin K in obstructive jaundice of only a few weeks' duration, whereas in intrahepatic jaundice (toxic or cirrhotic) there is no response or a very slow one.

In a series of cases with obstructive jaundice Herbert<sup>29</sup> reported that 68 per cent showed hypoprothrombinemia and in 30 per cent the titers fell below 50 per cent of the normal average. This author also reports cases of restoration of the plasma prothrombin level to normal after treatment with *Kapilon* in cases of biliary obstruction, and of failure of this treatment when there was damage to the hepatic parenchyma.

### Jaundice

Only quite recently has there been any change in the concept of the old term catarrhal jaundice. Now several reports have been made of such cases appearing in epidemic proportions among troops and civilian groups all over the world and a new term of *epidemic he-*

*patitis* or *infective hepatitis* has been coined to replace the older term of catarrhal jaundice.

Thus Cameron<sup>30</sup> reports studies on 170 cases of "infective hepatitis" observed in two army general hospitals in Palestine during 1940 and 1941. In these cases the minimum incubation period was about 32 days and the initial stages of the disease resembled sand fly fever, although typically not quite so severe. Initial severe anorexia was most striking and almost a diagnostic feature. Disinclination for smoking was common and nausea was frequent but vomiting rare. Abdominal discomfort with a tendency to constipation was the rule. Fever of a regular type between 99° and 103° F. was present in all cases during the preicteric stage. When jaundice appeared the initial symptoms rapidly subsided. The depth of the jaundice varied greatly, as did its duration. Usually it reached a maximum intensity at 5 days and had a range varying from 5 to 72 days. Bradycardia occurred with the onset of jaundice. Transient enlargement of the liver was noted in 97 of the cases and splenic enlargement was noted in 46 cases. Five points appear to be of major importance for diagnosis according to Cameron: anorexia, abdominal discomfort with or without hepatic enlargement and tenderness, absence of leukocytosis, increased urobilinogen in the urine, and histamine wheal test for latent jaundice. No deaths were reported in this series and recovery occurred in most patients after 35 days. The treatment included isolation of the patient and a minimum of one month's hospitalization. At the appearance of clay colored stools a **low fat and low cholesterol diet** was ordered. If stools remained acholic, **bile salts** were given so that fat could be introduced into the diet. On the theory that alcohol lowers

liver resistance all patients were kept away from alcohol for at least three months. Cameron concludes that the disease is due to a virus, but so far attempts at animal transfer have not been too successful.

Van Rooyen and Gordon<sup>31</sup> did not observe obstruction or catarrh of the biliary passages and therefore believe that the jaundice is toxic and due primarily to damage of the liver parenchyma. These authors are agreed that the disease is highly contagious and emphasize the necessity for treating it as a serious liver disease. They also believe the lowered general resistance, such as that which occurs so commonly in military campaigns, is a predisposing factor.

Civilian outbreaks of the disease have likewise been described. Thus Ford<sup>32</sup> has reviewed 300 cases which occurred in a suburb of London and reports one fatality from hepatic failure. The signs and symptoms, etc., were identical to the military reports, as were the conclusions. Water, milk, foods, and rodents were ruled out as a source of contagion and it was observed that personal contact seemed necessary to contract the disease.

An epidemic among school children and young school teachers has been described by Edwards<sup>33</sup> with practically the same findings, causes, and conclusions as in the report by Cameron.

Apparently the Germans too are bothered with so-called catarrhal icterus and epidemic hepatitis, for Dietrich<sup>34</sup> believes they are identical. He considers it an infectious disease, probably caused by a virus, which leaves a prolonged immunity and causes little serious trouble except an occasional cirrhosis or acute atrophy. He points out the prevalence of such a disease in many other wars; its incidence in the fall and early

winter months; its treatment as being merely symptomatic, and suggests the use of *convalescent serum*.

## INTESTINES

### Ulcerative Colitis

The rapid increase in sulfa compounds and improvement in surgical technic have brought about some improvement in the management of this important condition. This is particularly true of the so-called idiopathic, nonspecific variety; of bacillary dysentery; and of ulcerative colitis associated with lymphopathia venereum. Although the incidence of other forms of specific ulcerations of the bowel has been shown to be on the increase, nevertheless, to the writer's knowledge, little has been added of significance since the last careful review in 1941.

Bargen<sup>35</sup> has summarized his experiences with the various sulfonamides in the several ulcerative intestinal diseases. *Sulfanilamide*, *sulfathiazole*, and *sulfaguanidine* have all proved of value in the management of the intractable dense inflammation of the wall of the large intestine caused by the virus of lymphogranuloma inguinale. In this condition the combination of *sulfanilamide* orally up to 5 Gm. (75 gr.) a day for 3 or 4 weeks and the daily use of *sulfanilamide retention enemas* (about 4 Gm. [60 gr.]) daily has brought about surprising results. Good results have been obtained by the oral administration of 1.5 Gm. (22.5 gr.) of *sulfathiazole* 3 to 5 times a day for 3 weeks followed by the giving of 1 Gm. (15 gr.) 3 to 5 times a day for another 3 weeks. Courses of the drug are sometimes advised in resistant cases; that is, it should be given for 2 or 3 weeks with a rest period of one week before starting again. The administration of *sulfaguanidine* in doses of 10 Gm. (150 gr.) daily for

several months has been associated with progressive improvement.

*Sulfaguanidine* and *succinylsulfathiazole* seem to be the drugs of choice in bacillary dysentery and numerous articles have appeared indicating their value in all parts of the world. Again according to Bargen *sulfaguanidine* is best administered in doses of 1 Gm. (15 gr.) every 2 hours or 2 Gm. (30 gr.) every 4 hours, so that a total of at least 12 Gm. (180 gr.) is given every 24 hours. It is advisable to administer the drug for 2 weeks, to allow the patient a rest of 1 week, and to repeat the administration for a second 2 weeks, provided that untoward effects have not occurred.

Brewer<sup>36</sup> treated 77 cases with *sulfaguanidine* and reports complete cure in 73 per cent of the acute cases and 77 per cent of the chronic cases with very few toxic symptoms. Caldwell and Hardwick<sup>37</sup> reviewed observations on 357 cases of diarrhea in mental hospitals from 1940 to 1942 and report that *sulfaguanidine* appears to be an effective antidysenteric agent. They state that it clears the stools of *B. dysenteriae* quite rapidly and suggest that it may be an effective treatment for the chronic carrier. West<sup>38</sup> made a survey of 279 patients with diarrhea of which 167 were shown to have acute bacillary dysentery and his results with *sulfaguanidine* were excellent. Likewise, Lyon<sup>39</sup> treated more than 300 patients with "bloody flux" by giving an initial dose of 0.1 Gm. (1.5 gr.) per kilo body weight and then a maintenance dose of 0.05 Gm. per kilo every 4 hours. When the stools numbered less than 5 per 24 hours, the dose was decreased to 0.05 Gm. ( $\frac{1}{2}$  gr.) per kilo every 8 hours for 48 to 72 hours. If treatment was begun within the first five days of illness recovery occurred almost invariably in two or five

days. No toxic effects were observed on this program when an adequate urinary output was maintained.

Eisenoff and Goldstein<sup>40</sup> recently demonstrated the value of the sulfa drugs in bacillary dysentery. They studied an outbreak of Sonne dysentery involving 50 children in an orphanage having a total census of 145. Eighty-three of the children were proven by bacteriological survey to have positive stool cultures. Four of the *sulfonamides* were employed; *sulfathiazole* and *sulfadiazine* in doses of 0.065 Gm. (1 gr.) per pound of body weight, and *sulfaguanidine* and *succinylsulfathiazole* in doses of 0.130 Gm. (2 gr.) per pound of body weight. These drugs, when given in the prescribed dosages for an average of four days, cleared 90 per cent of the children with positive stools. The remaining 10 per cent were cleared after one or two additional courses of treatment. No advantages could be claimed for one over the other of these four drugs. It was observed that there was complete inhibition of growth of intestinal bacteria for a time in 80 per cent of all children treated with sulfathiazole, 70 per cent of those treated with sulfadiazine, 63 per cent of those treated with succinylsulfathiazole, and 37 per cent of all those treated with sulfaguanidine.

Smyth *et al.*<sup>41</sup> studied 28 cases of the Flexner type of bacillary dysentery and concluded that *succinylsulfathiazole* was just as effective as *sulfaguanidine*, and because it was without the potential toxic effects of sulfaguanidine it was the drug of choice in the treatment of such acute cases. They were able to effect a cure in 85 per cent of their cases by administering 0.25 Gm. (4 gr.) per kilogram initially and 0.25 Gm. (4 gr.) per kilogram daily for at least 6 consecutive days. If there was

no improvement after 3 days of this treatment the dosage was doubled.

The prophylactic use of *sulfaguanidine* in dysentery outbreaks has been frequently demonstrated. Lucchesi and Gildersleeve<sup>42</sup> gave 0.05 Gm. ( $\frac{1}{4}$  gr.) per Kg. of body weight every four hours for one day and then every eight hours for two days to 45 children exposed to dysentery without a single new case arising.

Scott<sup>43</sup> reports the absolute control of an epidemic of dysentery due to the Sonne type of dysentery bacillus in children by the use of 0.5 Gm. (8 gr.) of *sulfaguanidine* three times a day.

Clay<sup>44</sup> has reported the value of *sulfaguanidine* in bacillary dysentery and notes the reduction in the number of hospital days and Blumer and Priest<sup>45</sup> likewise mention this point. These latter authors have reviewed their cases of bacillary dysentery in the Middle East and conclude that sulfaguanidine is a specific drug in the treatment of acute, subacute, and chronic bacillary dysentery and estimate that its routine use would diminish the stay in the hospital by one-half. They found *sulfanilamide* of no value and *sulfapyridine* to be valuable but compared to sulfaguanidine too toxic.

So-called idiopathic or nonspecific ulcerative colitis represents by far the largest group of cases of ulcerative diseases of the colon. Considerable confusion still exists in proper terminology and etiology, but one of the earlier sulfa compounds is of great value, particularly if a strep is associated with the cause. Thus, *neoprontosil* in 3.24 to 5.83 Gm. (50 to 90 gr.) doses every 24 hours for a period of 2 weeks is in Barger's<sup>35</sup> experience still one of the most helpful sulfonamides. At the end of 2 weeks a rest period is advised and then another 2 weeks' course of therapy.

*Sulfaguanidine* in doses of 8 to 16 Gm. (2 to 4 dr.) a day administered with a rest period as for neoprontosil is also of value particularly, according to Mills and Mackie,<sup>46</sup> when there is little diarrhea. *Sulfathiazole* and *sulfadiazine* are both considered of value in these cases, cases, particularly according to Mills and Mackie who, in their study of *sulfathiazole*, *sulfadiazine*, and *sulfaguanidine* in 109 cases of ulcerative colitis, found improvement in 78 per cent. These authors state *sulfadiazine* has proved to be the drug of choice for all varieties of cases.

Bargen<sup>35</sup> believes that *succinylsulfathiazole* is the most recent drug that bids fair to be of help to some patients seriously ill with this disease, particularly when other drugs have been ineffective, or when it is desired to use a well tolerated drug that can be given in rather large amounts, or when patients have become sensitive to other forms. The drug is usually given in doses of 0.25 Gm. (4 gr.) per kilogram of body weight each 24 hours. Smaller doses of 1.5 Gm. (22.5 gr.) every 4 hours for several weeks have produced good results in Bargen's series.

The fact that the sulfonamides are potent drugs, and can be associated with deleterious effects to the human body, if administered in amounts greater than those required for therapeutic effects, is emphasized by Bargen.<sup>35</sup> For this reason careful studies of the chemistry of the blood should always accompany their therapeutic administration and frequent determination of the hemoglobin, erythrocytes, and leukocytes should be made. Furthermore, it must be remembered that the concentration in the blood of the various drugs required varies greatly for the therapeutic effect desired. Thus, for the average person 3.5 mg. per cent is an effective blood level for

*neoprontosil* and *sulfaguanidine*. However, for *sulfanilamide*, *sulfathiazole*, and *sulfadiazine*, about 10 mg. per 100 cc. of blood will be required for effectiveness. A concentration of about 2 mg. per cent seems effective for *succinylsulfathiazole*.

Since medical treatment for many cases of chronic ulcerative colitis is at times ineffective, and since at times radical surgical procedures are too drastic, Neumann<sup>47</sup> reports his results with *pneumoperitoneum* on seven cases. On the bases of weight gain, decrease in number of daily bowel movements, disappearance of mucus and blood from the stools, and the return of the individual to relatively normal activity, he reports excellent results. Five hundred cubic centimeters of pure oxygen were first used but later replaced by air. The therapeutic action is probably the result of mild irritation of the peritoneal surfaces, a mechanical action, and an indirect influence on the autonomic nervous system. No confirmatory reports of this work were observed, but it may be of use in medical failures before surgery has to be resorted to.

In those critically ill cases of ulcerative colitis that fail to respond to any form of medical therapy some way of putting the diseased area at rest must be attempted. *Ileostomy* is now considered the method of choice and the indications for this procedure are, according to Cattell<sup>48</sup>: (1) Acute fulminating cases, either in a first attack or with recurrent acute attacks; (2) medical failures, including those patients who are incapacitated; (3) massive hemorrhage; (4) subacute perforations, abscesses, peritonitis, or fistulas; (5) obstruction, and (6) polyposis including those cases with possible malignancy.

Bargen *et al.*<sup>49</sup> made a critical review of 185 cases where ileostomy had been



employed as a form of treatment for chronic ulcerative colitis. These 185 cases who suffered ileostomy for chronic ulcerative colitis at the Mayo Clinic in the 27-year period from 1913 to 1939 represented approximately 5.5 per cent of the total number of patients suffering from so-called chronic ulcerative colitis observed in that period. These writers comment that ileostomy is the only satisfactory method of diverting the fecal stream which is practicable and reasonably satisfactory. They point out that the immediate favorable response may be quite striking. This early gain in weight and general improvement usually wanes after the immediate postoperative period if the cases are followed closely and often the disease actually progresses. Consequently, few closures will ever be attempted, which implies that a *colectomy* will become advisable and, according to Bargaen's group, no one can or would advise such major surgery except for those patients who have complications or for the occasional intractable case. These authors conclude that when the condition of a patient suffering from ulcerative colitis reaches the stage in which ileostomy seems to be advisable or necessary, the performance of a colectomy subsequently should be seriously considered.

Cattell<sup>48</sup> presented three dictums for the closing of an ileostomy: (1) A clinical remission of symptoms should be maintained for an appreciable period. (2) The inflammatory process must be shown to have healed and be inactive as observed by the sigmoidoscope. (3) The colon must be shown to be distensible by means of a barium enema or double contrast air enema. However, he admits that the results, when the ileostomies were disconnected and continuity restored, were by no means satisfactory.

Of the nine cases that he reports only two have had complete relief from their disease. He concludes that closure seems possible in approximately 10 per cent of such ileostomies, but believes that if the indications for ileostomy are extended and if it is decided upon earlier, then the figure may be increased.

### Bacillary Dysentery

Some mention has already been made about bacillary dysentery because of the outstanding advances in its management by the newer sulfonamides. Several reports have appeared in the literature of rather extensive outbreaks of this disease in camps and among the patients and staff of military hospitals. Thus, Finlayson<sup>50</sup> reports two clinical types of "gastroenteritis" occurring shortly after the opening of a military hospital in South Africa. The one type was characterized by the passage of 3 to 20 liquid stools in 24 hours with complete recovery after about 48 hours. This type occurred among the bed patients and was found to be due to the *B. dysenteriae* Flexner group. The other type was usually ushered in by violent vomiting and frequent loose stools for seven or eight days. This type was noted among the staff and convalescent patients and found to be due to the *B. dysenteriae* Sonne. The source of the infection was traced to milk and cream which were neither pasteurized nor boiled. Finlayson believes that the so-called "infantile diarrhea" which is the chief cause of infantile mortality in South Africa is a form of dysentery and that the milk is contaminated by a milk handler who may be a carrier of dysentery bacilli. Another large epidemic of 400 cases has been reported by Green and MacLeod<sup>51</sup> with the conclusion that a dairyman concerned was in the habit of rinsing his sterilized bottles with cold

tap water and probably so started the infection.

Fairley and Boyd,<sup>52</sup> on the other hand, have made an extensive study of dysentery in the Middle East and conclude that most epidemics are fly-borne. The bacilli causing dysentery included the six Flexner and three Boyd strains as well as *B. dysenteriae* of Shiga, Schmitz, and Sonne types. They observed consistently disappointing results with *polyvalent antidyenteric serum* but with refined *antidyenteric Shiga serum* there was some often only temporary clinical improvement. Over 500 cases were treated with *sulfaguanidine* and a critical analysis of 96 Shiga cases led these authors to conclude that the drug was practically a specific cure.

It is of interest to note that not all types of bacillary dysentery respond to *sulfonamides*. Thus, an epidemic occurring in a large military camp in North Carolina is reported by Roberts and Daniels<sup>53</sup> in which *succinylsulfathiazole* was of no value. Two hundred and twenty-five soldiers ill with dysentery due to *Shigella paradysenteriae* Boyd—88 were studied with the conclusion that, since the illness was typically only of four days' duration, no amelioration was observed with the administration of succinylsulfathiazole. However, these authors did observe a reduction in the carrier rate, for when succinylsulfathiazole was given this rate was 2.6 per cent compared to 18.2 per cent in the untreated group.

Besides the outstanding values of sulfonamides in this disease some experimental and clinical evidence has been announced by Dotzer and Schuller<sup>54</sup> that the administration of *vitamin C* may be helpful as a prophylaxis and as a therapeutic measure in bacillary dysentery. This report seems rather weak and no confirmation was observed.

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## HEMATOLOGY

WILLIAM DAMESHEK, M.D.

### Introduction

Even wars, with all their carnage and destruction, have certain compensating values. The present world struggle is no exception. Aside from the purely technological advances which have been made, particularly in the fields of aviation and electronics, there are the accelerated developments in certain fields of medical research, particularly those dealing with shock, sudden changes in altitude, the therapeutic value of the sulfonamides and penicillin, and the use of blood and blood substitutes.

The development of the modern army hospitals, the numerous new diagnostic devices, and above all, the more precise knowledge—particularly in the laboratory—which the present generation of medical men possesses, have made the outlook of the wounded soldier immeasurably brighter. Not the least of these valuable features has been the very wide use of blood and blood substitutes.

During the early years of the first World War, relatively few transfusions of blood were given, chiefly because the application of Landsteiner's concepts of the blood groups (1900-1903) was slow

to develop. Among the first to sense the value of blood group determinations in transfusions was the group at Mount Sinai Hospital, New York. Ottenberg first suggested (1911) the use of universal donors, and Lewisohn was one of the first to use sodium citrate as an anticoagulant for the donor's blood.

In the decade following the end of the first World War, methods for transfusing blood were rapidly developed. The relative merits of whole unmodified blood and of citrated blood were being debated. Transfusions were serious affairs and generally performed by surgical teams in operating rooms. In 1927, the Russians, perhaps realizing the imminence of a new world conflict, set up a Central Institute for Blood Transfusion in Moscow, with separate decentralized institutes in various cities. By 1932, 80 of these institutes were in active operation and were equipped to take, give, and distribute blood to individuals in surrounding communities. Perhaps with an eye on the future war, research in methods for the preservation, administration, and storage of fresh and cadaver blood was actively carried on.<sup>1</sup> By

1941, when the Germans invaded Russia, 1500 transfusion institutes were in readiness for the quick distribution of blood at the front lines and in base hospitals far from the fighting scene.

The Spanish Civil War (1936-1939) served as a perfect setup, not only for the study of tank warfare, but for the clinical study of the various data on transfusions which had gradually been amassed. A large number of publications bearing on the storage and distribution of blood appeared, many of them in the British publication, *Lancet*. The Russians found that their citrate-glucose solution was a better preservative than citrate alone, that the universal donor could be used on a large scale in the front lines without further typing or cross-matching, and that undue hemolysis in the transportation of blood could be prevented by the use of isothermic containers. The aeroplane was furthermore found to be a far better means of transportation than the truck or train, apparently because of the lessened shaking and resultant hemolysis in the air than on the land.

Blood banks were inaugurated in this country at the Cook County Hospital and at the Philadelphia General Hospital. Their use spread rapidly, at first in the large urban hospitals, later in suburban institutions. In England, a closely integrated network of blood receiving, processing, and distributing centers proved of enormous value in the terrible days of the Blitz.

Simultaneously in this country, the use of plasma as a blood substitute was becoming recognized. An outgrowth of experiments on "lyophilization," dry plasma was shortly used for transfusions in cases of shock. The pooling of liquid plasma, the use of frozen plasma, and the development of albumin solutions, all came about rapidly under the impetus

of the second world struggle. In these developments the Americans have played a leading part.

### Blood Groups, Agglutinins, Etc.

**A Review**—Before discussing further the advances which have been made in the special fields of the agglutinins, hemolysins, and in the uses of blood and blood substitutes, it is essential to review our present knowledge of the blood groups.

Blood plasma or serum may or may not contain substances which are capable of agglutinating red blood cells. These substances, residing in the globulin fraction of the serum and whose exact nature is unknown, are called *agglutinins*. Conversely, red blood cells may or may not contain substances which are capable of uniting with agglutinin and thus becoming agglutinated; these substances are called *agglutinogens*. Agglutinin is thus present in the circulating plasma; agglutinogen in the red blood cells. Agglutinogens are also constituents of the various tissues of the body and appear to be complex carbohydrate-like substances. They have been isolated (Witebsky and Klendshoj)<sup>2</sup> from tissue sources and have the capacity of uniting with and inhibiting the activity of agglutinin. Humans have in their tissues and red cells either A agglutinogen, B agglutinogen, both agglutinogens—AB, or neither—O. Thus humans can roughly be divided into four blood groups, according to the type of agglutinogen present in the red cells: A, B, AB, and O. This, the so-called International type of designation, should replace the previously used, often confused, and rather meaningless Moss and Jansky classifications of I, II, III, and IV.

Agglutinogens have the capacity of acting as antigens; *i.e.*, they can cause

immunization with the subsequent development of antistances or agglutinins. Thus A agglutinin, when repeatedly injected, may result in the development of anti-A agglutinin. Curiously, and for no reason which seems readily apparent, A agglutinin in the red cells co-exists with anti-B agglutinin in the plasma and conversely B agglutinin with anti-A agglutinin. The combinations are as follows:

Agglutinin (in red cells)	Agglutinin (in plasma)
A	Anti-B
B	Anti-A
AB	No agglutinin
O	Anti-B, Anti-A

Obviously, this is the way it should be, since if anti-B agglutinin were present together with B agglutinin, intravascular agglutination would occur. In any event, an individual of group A (*i. e.*, whose red cells contain A agglutinin) cannot receive blood from a group B individual without serious trouble—not because A cells and B cells will not mix, but because anti-B agglutinin in the A individual's plasma will react with the introduced B cells with resultant agglutination. That is why an O individual, whose red cells contain no appreciable agglutinin can receive blood only from O donors, since his own blood contains both types of agglutinins, anti-A and anti-B.

It was for many years thought that red cells contained only the two major agglutinogens, A and B. However, subgroups and other factors in the red cells have gradually been uncovered:<sup>3</sup> the A1 and A2 subgroups, the M and N agglutinogens, the P factor, the H factor, and more recently the Rh agglutinin (or factor). Except for the A1 and A2 agglutinogens, these substances exist in the red cell without relationship to other agglutinogens which may be present.

Thus a red cell may contain agglutinogens A, Rh, M, N, and P, or it may be relatively free of agglutinogens, as in the case of O, Rh negative individuals.

Agglutinogens are inherited according to Mendelian law. Thus, the mating of an A, Rh, M individual with one who is A, Rh, M cannot result in an offspring who is B, Rh negative, N. For this reason, the determination of the various blood group factors, more particularly the M and N agglutinogens, becomes distinctly important in medicolegal work, particularly in paternity (bastardy) cases.

Agglutinogens may or may not be antigenic in the same species, *i. e.*, they may or may not be capable of producing agglutinins (iso-antibodies). Thus, the M and N agglutinogens may be given with impunity in repeated human transfusions without development of anti-M or anti-N agglutinins. However, animals may develop antibodies to M and N agglutinogens, *i. e.*, *hetero-immunization*. In infectious mononucleosis, the blood serum usually develops an agglutinin which reacts with *sheep's* red cells; this is a *hetero-agglutinin*. Conversely, the Rh agglutinin is a potent antigen from human to human; repeated transfusions from Rh positive individuals to Rh negative recipients often result in the development of an anti-Rh agglutinin; this is an *iso-agglutinin*.

The universally present anti-A and anti-B agglutinins react with agglutinogens A and B in a wide temperature range; *i. e.*, the reaction takes place at room temperature (approximately 20° C.), at ice-box temperatures (0.4° C.), and at incubator temperature (37° C.). The activity of some agglutinins is best manifest at incubator temperature; these are called *warm* agglutinins, *e. g.*, the anti-Rh agglutinin. Some agglutinins have their greatest activity, however, at

lower temperatures—room or even ice-box; these are *cold* agglutinins.

**Methods for Determination**—The ordinary blood groups are readily determined by the use of anti-A and anti-B typing serum. The use of high titer sera is naturally to be recommended, since sera of low titer may show no agglutination with a weak agglutinin, particularly A. Thus, certain individuals who have been typed as O or B may be, respectively, A or AB. High-titer serum may now readily be obtained.\* In addition, serum concentrates, powdered serum, and serum fractions, have been or are being developed. Dry anti-A and anti-B testing powders\*\* keep well in a wide temperature range and give a very quick reaction which can quite readily be seen on a slide with the naked eye. Confirmation of the test can be made with the low power microscope. Since agglutinins are chiefly found in the globulin fraction of the plasma, fractionation has recently been utilized by precipitation of the albumin fraction with methyl alcohol.<sup>4</sup> The globulin fraction can then be concentrated and this lends itself well to blood grouping purposes; complete gross clumping takes place in 60 seconds.

Although the regular blood groups (agglutinogens) can readily be determined on a glass slide at room temperature, this method is not to be recommended for compatibility tests, in which one wishes to note whether the recipient's blood contains an agglutinin which may react with the recipient's red cells. The slide test for compatibility is: (a) frequently not sufficiently sensitive in the detection of normal and abnormal agglutinins of low titer, and (b) of little value in the detection of a warm agglutinin, more particularly the anti-Rh ag-

glutinin, and (c) gives a reaction of so-called incompatibility in the presence of a cold agglutinin. For these reasons, the Landsteiner-Levine test tube technic at incubator temperature (37° C.) is to be preferred.

**Method**—Small test-tubes (7 x 21 mm. *i. e.*, "Hinton" and "Kahn" tubes) are used. One drop of serum to be tested, one drop of a 2 per cent red cell suspension, one drop of normal salt solution are placed in the tube, mixed, and placed in the incubator for at least 30 minutes. The tube is removed and centrifuged at very slow speed for one minute. The "button" may be examined with a hand lens for the presence or absence of agglutination. The tube is then shaken and examined for macroscopic agglutination. Confirmation of the presence or absence of agglutination is obtained by examination of some of the tube's contents on a slide with the low power of the microscope. This method, although seemingly complicated in its description, is readily performed in simple laboratory set-ups and is sufficiently sensitive for the detection of the great majority of normal and abnormal agglutinins of low titer, including the anti-Rh agglutinin.

The one possible disadvantage of the routine use of the above technic is that it fails to detect cold agglutinins, which have recently assumed some diagnostic importance. This disadvantage may be obviated by performing simultaneous compatibility tests at either room or, preferably, ice box temperatures. For routine transfusions, it matters little whether the recipient's blood contains a cold agglutinin, providing relatively warm blood is used; however, the finding of "incompatibility" due to the appearance of agglutination in the slide-cross-matching technic at room temperature has often held up the use of transfusion in patients desperately ill with acute hemolytic anemia.

### **The Rh Agglutinin (Factor) and the Anti-Rh Agglutinin**

The development of knowledge regarding the Rh agglutinin and its relation

\*Blood Betterment Association, New York City.

\*\*Lederle Laboratories.

to transfusion reactions and to acute hemolytic anemia of the newborn (erythroblastosis foetalis) has made one of the most fascinating and important chapters in modern medicine. In searching for factors in the red blood cell other than those previously described as A1, A2, M, N, H, T, etc., Landsteiner and Wiener injected the red cells of the *Macacus rhesus* monkey into rabbits and guinea pigs, thus producing an anti-monkey (anti-Rh) serum which had the ability to agglutinate monkey red cells in the test tube. This was to be expected, but the unexpected (although perhaps hoped for) development was the finding that this anti-monkey red cell serum agglutinated the red cells of 85 per cent of all *humans* tested; 15 per cent showed no agglutination. In other words, 85 people out of 100 tested must have in their red cells a "monkey" factor or agglutinin which was capable of reacting with the anti-Rh agglutinin or factor, *i. e.*, they were Rh positive. Fifteen per cent did not possess this Rh agglutinin or factor, *i. e.*, were Rh negative.

At about this same time Philip Levine of Newark, in studying severe and often fatal transfusion reactions in certain women in childbirth, discovered a warm agglutinin in their blood sera. Taking advantage of the newly-developed knowledge regarding the Rh agglutinin, he found that the women in these cases were Rh negative and the husbands Rh positive. Was it possible that the husbands had immunized their wives to the Rh factor by means of the fetus, with the result that an anti-Rh factor had developed? Subsequent studies bore out this hypothesis and showed furthermore that the Rh factor is inherited as a Mendelian dominant; the children of an Rh minus, Rh plus mating, are for the most part (50 to 75 per cent) Rh plus; the placenta

can apparently transmit Rh substance from the fetal to the maternal circulation; an antibody, the anti-Rh agglutinin often develops in an Rh negative mother.<sup>5</sup> This does no particular harm to the mother or the mother's red cells, but should a transfusion be required and an Rh positive donor (even of the same blood group) be used, a severe and perhaps fatal reaction might develop as the result of the interaction of the mother's anti-Rh agglutinin and the Rh agglutinin in the transfused red cells.

Levine and his co-workers found that the anti-Rh agglutinin of humans was identical with that induced in animals by the injection of monkey red cells. They, furthermore, showed that the human agglutinin was even stronger and more regular in its effects and that it was chiefly a warm agglutinin,<sup>5</sup> rather than a cold agglutinin as Wiener had at first thought.

Levine's studies of the transfusion reactions of certain mothers in delivery naturally led him to the study of infants dying of hydrops, erythroblastosis foetalis, etc., since it appeared that the two sets of circumstances were often co-existent. As a result of this work, it was shortly established that in acute hemolytic anemia of the newborn the following combination of factors is almost always present: the mother is Rh—; the father is Rh+; the child is Rh+; the mother frequently showed an anti-Rh agglutinin. Putting these facts together, it appeared likely that, by the passage of red cells themselves or of Rh agglutinin substance through the placenta, the fetus *in utero* immunized the mother with the Rh agglutinin which had been inherited from the father. The mother developed an anti-Rh agglutinin which, passing back through the placental circulation, reacted with fetal red cells, chiefly it would appear, at the time of birth with the result that an agglutina-



tion-hemolysis reaction developed in the infant's circulation. The end-result has for years been called erythroblastosis foetalis, but is probably better known as acute hemolytic anemia of the newborn.<sup>6</sup>

Further studies have demonstrated the correctness of these original assumptions as explanatory of at least 90 per cent of all cases of acute hemolytic disease of the newborn. It is probable, however, that other agglutinins, or perhaps such physical factors as the condition of the placenta, have some bearing in a few cases. The lack of erythroblastosis foetalis in some infants born of Rh—, Rh+ matings may depend upon the father's genotype, *i. e.*, an Rh plus phenotype is made up of either genotypes RhRh or Rhrh. From the latter genotype, the infant may inherit either dominant Rh or recessive rh. If the latter, the union of recessive gene rh with the mother's rh results in an rh negative infant's blood.

The low incidence of erythroblastosis foetalis in the colored and Chinese led Levine and Wong<sup>7</sup> to study the incidence of the Rh factor in these groups. Although 15 per cent of whites are Rh negative, only 5 to 8 per cent of the colored groups tested with Rh—, and only one of 150 Chinese tested was Rh—. (It should immediately be pointed out to those who pride themselves on the lack of the "monkey" factor Rh in their red cells that its absence does not necessarily preclude the possibility of the presence of, say, a baboon or an orang-outang factor. Studies of human blood for such factors has not yet been undertaken.)

Determination of the Rh factor is of importance in at least three conditions: (1) In pregnancy and childbirth when a transfusion is contemplated for severe anemia or shock; (2) in acute hemolytic anemia of the newborn, and (3) in re-

peated transfusions. In the latter, if the recipient is Rh negative, repeated transfusions of blood, even of the same group, will almost certainly result in the development of an anti-Rh agglutinin; thus, after three to six or more transfusions, the next transfusion, if Rh positive, may result in a severe and perhaps fatal hemolytic reaction.<sup>8</sup>

For determination of the Rh factor, a potent anti-Rh serum must be available. As yet, such sera are difficult to obtain, because (a) the regular production of potent anti-Rh agglutinin in animals has proved very difficult, and (b) high titer anti-Rh sera are only occasionally found in the mothers of infants with erythroblastosis foetalis. It is advised that each mother of such an infant should routinely be tested for anti-Rh agglutinin and if this is present, even at low titer, she be bled 50 to 100 cc. Concentration of serum can later be performed. Methods for doing this are now in process of development.

The test for Rh factor is performed by the Landsteiner-Levine technic at 37° C. as above described. It is important to use dilute (1 to 2 per cent) red cell suspensions. Levine<sup>9</sup> and co-workers have found three types of anti-Rh serum: one agglutinating 87 per cent of white individuals (anti-Rh 1, 2), another agglutinating 85 per cent (anti-Rh), and the third agglutinating 73 per cent (anti-Rh 2). Since the latter serum gives 27 per cent negative reactions, the significance of an Rh negative determination in a given case is open to doubt. Thus, unless a laboratory has a highly potent anti-Rh testing serum, it is important to perform a very careful compatibility test of the recipient's serum with the prospective donor's red cells. To do this, the time of incubation may be prolonged to one hour. Boorman, Dodd, and Mollison<sup>10</sup> suggest a modi-

fication of Levine's technic which they state brings out a greatly increased evidence of the anti-Rh agglutinin. These workers allow the mixture of recipient's serum, donor's red cells, and normal salt solution to remain in the incubator for two hours. The pattern of the sediment is then examined with a hand lens and a portion is pipetted off for microscopic examination. They state that the manipulation of the blood involved in centrifugation and shaking may abolish a weak reaction. If such tests are negative, the transfusion may be given with almost complete safety. The reservation must nevertheless be made that even with a completely negative *in vitro* test, there may be an *in vivo* hemolytic reaction. The only possible way to obviate this completely is to set up a list of well-established Rh negative donors for use in the three conditions referred to above, *i. e.*, in women in childbirth, in erythroblastosis foetalis, and with repeated transfusions. It is almost essential to use nothing but Rh negative blood in infants with acute hemolytic anemia, since transfusions are the only treatment, and the introduction of Rh positive cells may result in the combination with any still present anti-Rh agglutinin derived from the mother.

### Cold Hemagglutinins

The antigen-antibody reaction between human red cells and serum which is observed either chiefly or solely at temperatures below 20° C. is called cold hemagglutination. Cold agglutinins in low titer are commonly present; thus, Kettel found them in 95 per cent of normal individuals, and more recently Shooter,<sup>11</sup> in examining 4710 sera, found that 32 per cent showed these antibodies at 5 to 7° C. However, cold agglutinins sufficiently strong to be active at room temperature were found in only 29 of

10,000 sera. Low temperatures at times activate or bring to light an otherwise weak agglutinin; this is reminiscent of the Donath-Landsteiner phenomenon: the activation by cold of the abnormal hemolysin of paroxysmal cold hemoglobinuria. The subject of cold hemagglutination is an old one, having been discussed by Landsteiner in 1903 and more fully by Landsteiner and Witt in 1926. Although cold hemagglutinins have been observed in such diverse diseases as cirrhosis of the liver, hemolytic anemia of the acquired type, and in infections due to spirillae and the trypanosomes, interest in this subject has been considerably enhanced in the past year by the finding of such agglutinins of high titer in primary atypical (virus ?) pneumonia.<sup>12, 13</sup> The initial hope that this antibody would prove of diagnostic importance in the differentiation of atypical from other pneumonias has proved only partially correct, since a high titer is present initially in only about 50 per cent of all cases. The titer of agglutinin frequently increases with progression of the disease and may reach its peak in seven to 14 days.

The cold hemagglutinin appears to be quite distinct from the normal blood agglutinins since it agglutinates all human red cells, even those of Group O, and may agglutinate those of a number of animals (*i. e.*, "panagglutinin"). Because this agglutinin has also the property of agglutinating the red cells of its own blood (at least in the test tube), the term *auto-agglutinin* has often been used. This, however, is only partly descriptive and it is probably best to use the more general term cold hemagglutinin.<sup>14</sup>

Aside from the purely diagnostic one, the cold hemagglutinin has recently assumed considerable clinical importance. Thus, certain cases of acute hemolytic anemia at times occur in association with

primary atypical pneumonia. Usually, although not always, the sulfonamide drugs have been administered and it has been customary to ascribe the hemolytic reaction to the drug.<sup>14</sup> Whether or not this is correct, when a transfusion is considered for the severe anemia, and blood grouping tests are done, it is often found that all prospective donors are "incompatible." This is, of course, due to the presence of cold agglutinin in high titer with resultant agglutination—at room temperature with the ordinary slide technic—of the red cells of all blood groups. For this reason, transfusions have often been delayed for long hours in patients desperately needing them. In such an event, the matter is quickly resolved by performing the cross-matching at incubator temperature by the test tube technic above described. The author has also recommended in such cases the use of blood which is kept warm from the time of its removal from the donor to its entrance into the blood stream of the recipient.<sup>14</sup>

The cold hemagglutinin in these cases is also important from the standpoint of chilling of the patient. Thus, in a recent report,<sup>15</sup> marked acrocyanosis and beginning gangrene of the nose, ears, and fingertips is described in association with primary atypical pneumonia and a high titer of cold agglutinin. The cold agglutinin may persist for months or perhaps years following an attack of atypical pneumonia, making the individual who harbors it liable to the development of: (a) Hemoglobinuria; (b) chronic hemolytic anemia; (c) extreme coldness and blueness of extremities, or (d) even gangrene upon exposure to extreme cold. In a case under study at the present time,<sup>16</sup> all of these symptoms have been present since an attack of pneumonia two years ago. Two or three further attacks

have occurred in the interim. The cold hemagglutinin is present in a titer of 1:128,000! Because of the presence of a chronic hemolytic anemia with splenomegaly, it is likely that he has considerable *in vivo* auto-agglutination which is enhanced by exposure to cold. Daniel Stats and J. G. M. Bullowa<sup>17</sup> report a somewhat similar case in which symmetrical gangrene of the tips of the extremities occurred with exposure to cold. This patient did not have a hemolytic process but the *in vivo* agglutination of red cells could be demonstrated by introducing ice water into the conjunctival sacs and examining the bulbar and palpebral conjunctivae with the slit lamp corneal microscope.

From these and other observations come several morals: (1) Patients with primary atypical pneumonia should under no circumstances be chilled. (2) If a transfusion should become necessary because of an acute hemolytic reaction, the cross-matching should be done by the test tube technic at incubator temperature. (3) Warm blood should be used and the apparatus, tubing, etc., should be kept constantly as warm as possible. Cold blood withdrawn from the refrigerator should not be used, certainly not before proper warming.

### Other Abnormal Agglutinins

**Hemolysins** — Isoagglutinins other than the anti-Rh and the cold agglutinin of primary atypical pneumonia are only occasionally encountered. Repeated transfusions of an individual of blood group A may be followed by severe reactions. These are probably due to isoimmunization by either the A1 or the A2 factor with subsequent development of an anti-A1 or anti-A2 agglutinin. Since the latter agglutinin has the added peculiarity of reacting even more strongly with

group O blood than with A2 blood, this possibility should be kept in mind in the presence of a transfusion reaction when O cells are used. The differentiation of A1 from A2 cells is discussed in the excellent manual on *Blood Grouping Technique* by Schiff and Boyd.<sup>18</sup>

Other peculiar and not readily classifiable agglutinins are occasionally found in the acquired forms of hemolytic anemia. Cold hemagglutinins (often called autoagglutinins) have frequently been found in these cases. In fact, Widal and his co-workers stated that this finding was of diagnostic importance in such cases. Also found in occasional cases of acquired hemolytic anemia of unknown etiology are isohemolysins. These are of the immune body variety: being inactivated by heating the serum to 56° C. and reactivated by the addition of guinea pig complement. Dameshek and Schwartz believed that this hemolysin, which hemolyzed the cells of all blood groups, including O, *in vitro*, might be etiologically related to the disease process (*i. e.*, was an autohemolysin). In cases of acute hemolytic anemia particularly, search for such hemolysins should routinely be made; in the second case of this series, it was at first impossible to match a compatible donor because of the complete hemolysis which occurred when the patient's serum was added to prospective donors' red cells. The peculiar hemolysin of another more chronic hemolytic anemia known as paroxysmal nocturnal hemoglobinuria or the Marchiafava-Micheli syndrome may be the cause of the severe reactions which often occur when transfusions are given to an affected patient. Because of the possible presence of these abnormal agglutinins and hemolysins, particular care should always be taken in the cross-matching of blood in cases of hemolytic anemia.

### Transfusion Reactions

Severe and often fatal transfusion reactions still occur all too frequently. Exact statistics on their incidence are almost impossible to obtain because most of them go unreported. They are probably as common as they are because blood grouping is today often relegated to inexperienced individuals with little awareness of the great responsibilities involved in correct typing and cross-matching. The development of a fatal transfusion reaction in a relatively healthy young person who is being prepared for an elective operation is a tragic event which is in many instances due to omission of either the typing or the cross-matching test. Each transfusion should be preceded by (1) careful cross-matching of the recipient's serum with the prospective donor's red cells suspension, and (2) typing of both the recipient and the prospective donor. Except under very special circumstances, it is not necessary to do the so-called minor agglutination—*i. e.*, the donor's serum *vs.* the recipient's red cells. If the same blood groups are used, no agglutination will occur with the donor's red cells; if a group O donor is, for example, used for a group A recipient, the resultant agglutination with the donor's red cells is to be expected because individuals of group O have anti-A and anti-B agglutinins in their sera.

As noted above, cross-matching should preferably be done by the test tube technique at incubator temperature, and for at least 30 minutes. This has recently been officially recommended by the (British) Medical Research Council.<sup>19</sup> If an unusual emergency exists and 30 minutes seems too long a period to wait, blood plasma should immediately be given. (cf. below.)

*False negative* agglutination tests may be obtained because of the use of low

titer testing sera; this is particularly true of anti-A sera which do not react with cells of A2 and A2, B groups. Serum which has become infected may also give negative results. *False positive* results are often a matter of interpretation. The most common error is to confuse *rouleaux formation* with agglutination. Red cells aggregate in rouleaux because of the action of a substance in the globulin fraction of the plasma. In the presence of infection, this substance becomes greatly increased, as a result of which rouleaux formation becomes considerably enhanced. This is brought out in the sedimentation reaction, which in the case of infections becomes greatly increased due to the rapid fall of the large aggregations of cells in the sedimentation tube. Microscopically, the plasma or serum from a case with severe infection results in the aggregation of red cells of all blood groups in long rows like piles of coins. This is quite distinct from the picture of agglutination in which the red cells are grouped together in clumps resembling a pile of marbles stacked one upon the other. Since strong rouleaux formation has often resulted in a report of "incompatibility," it is important to make the differentiation of rouleaux formation from agglutination. This can usually be made with certainty by diluting the serum half and half with normal salt solution; the aggregation factor is thus sufficiently diluted so that rouleaux formation is reduced to a minimum. Aggregation is further diminished by tapping the slide while it is being microscopically inspected. Agglutination is not inhibited either by dilution or shaking.

Cold agglutination (cf. above) has become an increasingly important cause of false incompatibility reactions. Infected cell suspensions and sera may also result in false positives.

The moral of all the foregoing is that the transfusion reaction is best treated by its prevention. The interne or the technician who performs the tests must be aware of the important responsibility involved—literally one of life and death. Both typing and exceedingly careful cross-matching must be done. False negatives and positives should be known about. Even in an emergency, carelessness and too much hurry are inexcusable. While the clinician is waiting upon the laboratory for the report of a test for compatibility, the intravenous administration of salt solution and/or plasma can well be begun.

Finally, it should be realized that even with all the foregoing precautions carefully observed a reaction may nevertheless occur. In other words, the *in vivo* biological test is at times more accurate than any and all *in vitro* testing. For this reason, the recipient should be carefully watched, particularly during the administration of the first 50 to 100 cc. of blood. If there is any complaint whatever of pain in the back or flanks, pain down the legs, a smothering sensation, a burning sensation in the face, a sense of constriction, a chilly sensation or chill, or even a sense of "something wrong," the transfusion should be immediately discontinued. These symptoms are usually indicative of intravascular agglutination. Whereas the recipient can survive the administration of 50 to 100 cc. of incompatible blood, the agglutination of 500 cc. of blood is usually fatal.

Intravascular agglutination leads to two distinct phenomena: (1) Hemolysis, and (2) blockage of renal glomeruli with agglutinated red cells. The rapid hemolysis of agglutinated red cells results in almost immediate hemoglobinuria which, when it exceeds the normal threshold of about 150 mg. per 100 cc., is followed by

hemoglobinuria. As hemolysis continues, bilirubin is formed in excessive amounts with resultant jaundice, and an abnormal blood pigment—methemalbumin (Fairley)—is produced. But the chief danger is not the excessive hemolysis, but rather the blockage of glomeruli with agglutinated red corpuscles, and the blockage of renal tubules with insoluble acid hematin casts. P. L. Mollison<sup>20</sup> has discussed this subject at length. In the presence of an acid renal tubular excretion, excreted hemoglobin is modified to methemoglobin and acid hematin with the resultant precipitation of insoluble acid hematin casts. The first evidence of this is failure of the patient to pass more than a few cc. of urine. There is then increasing evidence of renal failure with rising blood urea and nonprotein nitrogen values, the patient finally becoming uremic and comatose. Although death usually occurs, in some instances the patient suddenly begins to pass a good deal of urine and recovery ensues.

The investigation of a hemolytic transfusion reaction has been described by Mollison.<sup>20</sup> This involves the re-grouping and re-cross-matching of both recipient and donor; testing both for Rh factor; determination of abnormal agglutinins or hemolysins in the recipient's serum; titration of the donor's serum for agglutinins; examination of both a pre- and a post-transfusion sample of the recipient's blood. If no abnormalities of sufficient etiologic importance to result in a severe hemolytic reaction are found, the possibility of the introduction of cells from another donor must be considered; this is a definite possibility in blood banks. If such a consideration occurs, recourse may be had to the differential agglutination test, in which a red cell suspension of the recipient is tested respectively with high titer anti-A and

anti-B sera for the degree of agglutination. This may be quantitatively carried out in a hemacytometer.

The treatment of a severe hemolytic transfusion reaction is often thankless but should nevertheless be carried out with vigor, because of the perhaps one in ten chance of recovery. Fluids should be forced, both by mouth and intravenously. A constant intravenous drip should be set up and normal salt solution and 5 per cent glucose given alternately. Five thousand cubic centimeters of intravenous fluids daily is by no means a large amount. The use of alkalization has been suggested by de Gowin *et al.*, the rationale being that in an alkaline urine, plasma hemoglobin is converted to oxyhemoglobin and the tendency for the development of precipitated hemoglobin and hematin is greatly reduced. Alkalinization may be carried out by the use of 5 per cent sodium bicarbonate solution given intravenously by the intravenous drip. One thousand to 1500 cc. may be given once or twice during the 24-hour period, either alone or simultaneously with the normal salt or dextrose solution by means of a Y-tube connection. Hypertonic 25 per cent, or even 50 per cent, glucose solution may be used in the attempt to stimulate urinary excretion through a swollen kidney; this is of questionable value. If the patient's life is in jeopardy not only because of the reaction but because of severe anemia, another transfusion may well be attempted—providing, of course, that all possible precautions for incompatibility are carefully observed. This has occasionally been lifesaving, particularly in acute hemolytic anemia. Decapsulation of the kidneys and sympathectomy have been suggested in the attempt to allow a congested kidney somehow to release itself and produce urine; the results of these methods are questionable.

One should reiterate over and over that the best way to treat a transfusion reaction is to prevent it. Don't give a transfusion unless it is absolutely essential! Type and cross-match properly, with due regard to the responsibilities involved! Watch carefully for an *in vivo* reaction and discontinue the transfusion immediately should even a questionable reaction occur.

### Whole Blood

#### The Use of Fresh Whole Blood—

The first transfusions were given with fresh, whole, unmodified blood. This required either a direct arteriovenous connection or the use of waxed cylinders, multiple syringes, special valves, etc. The development of the citrate transfusion was a great step in advance. Although the supposed virtues of "unmodified" blood are still sung by some, it can now be said: (a) That citration does no harm; (b) that it does not reduce the numbers of platelets or modify any special physiologic principle of red or white cells, and (c) it makes transfusions a simple bedside maneuver. A bad feature of this unusual simplicity has been the great promiscuity in the use of transfusions, which have now become almost as common as was blood-letting a century ago.

The actual indications for transfusions of whole blood are few. They may be tabulated as follows:

#### 1. *Blood Dyscrasias*

Severe anemia:

post-hemorrhagic hemolytic aplastic, dysplastic rarely in deficiency states.

Severe thrombopenic hemorrhagic states: hemophilia, hypoprothrombinemia, thrombopenic purpura.

Severe leukopenia:

questionable value.

2. *Severe Hemorrhage*—Generally over 1000 cc. Plasma may be initially used (see below).

3. *Shock*—Plasma is better here, but whole blood may be used if plasma is not available.

4. *Certain Infections*—To aid immune processes (?) by supplying antibody or other material.

In transfusions, it is best to give the recipient blood of the same group. This is particularly important in cases of severe anemia, more especially in hemolytic anemia. In these cases, the relatively small amount of agglutinin introduced with the donor's blood may be sufficient to cause agglutination (and hemolysis) of the recipient's red cells which are relatively few in number or already injured (as in the presence of spherocytosis).

Although most authorities are agreed that universal donor blood (Group O) should be used only with Group O individuals, a strong case for their use with other groups has been made by N. Rosenthal and P. Vogel.<sup>21</sup> Ottenberg in 1911 first suggested the use of universal donors and this practice has since then been continued at the Mount Sinai Hospital (New York) for urgent transfusions and for patients whose specific blood group was not available. Rosenthal and Vogel<sup>21</sup> point to the widespread use of the universal donor in France and Belgium, where such donors are considered preferable because no time is lost in starting the transfusion, both grouping and cross-matching being omitted. The emergency transfusion service of Paris supplied donors for 6000 transfusions annually without the report of a fatal reaction. The above authors report on 819 carefully observed transfusions in which Group O blood was used for recipients of Groups A, B, and AB; the incidence of reactions was no greater than with the use of homologous blood. Indications for such use of the universal donor were either under conditions of urgency, as in postoperative shock, acute blood loss, etc., or when other homologous donors were not available.



The chief objection to the use of universal donor blood is the presence of a possibly high titer of agglutinin, which according to Coca occurs in 3 per cent and according to Hesse in 30 per cent of all Group O donors.<sup>22</sup> Because of this an amendment has been made to the Sanitary Code of the State of New York which requires the serum of Group O donors to be titered for agglutinin content. The agglutinins can, however, be neutralized by the addition of the isolated blood group specific substances, A and B, as suggested by E. Witebsky, N. D. Klendshoj, and Paul Swanson. The A and B agglutinogens have been found not only in the red cells but in saliva, the gastric juice, various tissues, etc. From these sources, carbohydrate substances have been isolated which are specific in neutralizing anti-A and anti-B agglutinin. Thus, Witebsky found that 25 mg. or less of A substance could neutralize all the anti-A agglutinin present in 500 cc. of O blood. The A and B substances, which are now clinically available in solution, may be added in precise amounts to O blood prior to transfusion and will cause neutralization of the agglutinins present.

It is best to reserve the use of O blood for individuals of Group O and for individuals of the other blood groups under certain emergency situations. Even then, if the recipient is very anemic, and particularly if hemolytic anemia is present, blood from a homologous donor should be used. It is conceivable that on the battlefield a great saving in time and possibly life may occur if squads or platoons of Group O individuals are present in each company; in emergencies these individuals may be used without typing and cross-matching for transfusing their wounded comrades. It is reported that the Russians have successfully used this technic. Even under such condi-

tions, however, one may wonder whether it is not best to use plasma, which is often more readily available, more quickly given, and perhaps of greater physiological value.

**Whole Bank Blood**—The use of whole "bank" blood has spread rapidly with the establishment of numerous blood banks, first in large municipal hospitals, then in suburban institutions, and more recently even in relatively small community hospitals. The blood is obtained either from voluntary donors, from relatives and friends of patients currently in the hospital and requiring transfusions, or from patients requiring venesections: cardiacs, polycythemics, etc. Although the use of placental blood was enthusiastically urged a few years ago, its present application seems small. In this country, 50 cc. of a 2.5 per cent citrate solution is routinely used as an anticoagulant for 500 cc. of blood. Because of their greater storage value, more or less complex solutions containing glucose as well as citrate have been recommended in Russia and to some extent in England. With each bottle of blood, it is customary to fill two tubes, one for serological testing for syphilis, the other a "pilot" tube, which can be used for determination of blood group, cross-matching, and culture. The blood bottles are immediately placed in a refrigerator which can maintain a constant temperature of about 4° C. When the blood group and serology are determined, a suitable tag—often of different colors for different groups—is affixed to the bottle. The bottles of the different blood groups can be stored on different shelves of the refrigerator.

Refrigeration decelerates but does not prevent the development of certain changes which always occur when blood is allowed to stand. These changes must be constantly kept in mind in the use of

whole bank blood. The red cells become swollen, thicker, and rounder, *i. e.*, spherocytic. With increasing spherocytosis, the hypotonic fragility becomes more and more increased. After 10 to 14 days' storage of citrated blood, the red cells may hemolyze even in normal salt solution. At the end of two weeks, grossly visible hemolysis is usually present. With the glucose-citrate solutions, these changes in the red cells occur more slowly, so that gross hemolysis may not be present for three to four weeks. The red cells also undergo certain chemical changes, *i. e.*, they take on glucose from the plasma (glycolysis), and they lose potassium, which accumulates in the plasma. These changes have been carefully studied by Jorda, Scudder, deGowin, and others.

The leukocytes quickly diminish; within 24 hours, their number is halved; in a week, perhaps only 10 per cent of the original number is present. The quick development of degeneration may be noted in blood smears, which show increasing toxic granulation, the development of vacuoles, etc. The platelets diminish quickly in stored blood and at the end of 72 hours are hardly visible.

Modification of the blood plasma also gradually occurs. The diminution in blood sugar and the increased potassium content have already been alluded to. More important perhaps is modification in the plasma globulins, because it is in this portion of the plasma that immune bodies, enzymes, blood clotting factors, etc., are found. Certain factors like prothrombin—which lends itself to ready study—have been investigated. There is a gradual, although slow, loss of this material in stored blood, the concentration being reduced about 30 per cent in two weeks.<sup>23</sup> The globulin factor (? thromboplastin) lacking in hemophilia probably disappears rather quickly, as

do certain enzymes, immune bodies, complement, etc.<sup>24</sup> The electrophoretic patterns of normal and preserved blood have been studied by Scudder. The blood albumin factor of the plasma appears to be more stable and survives months of storage. With increasing hemolysis, there is naturally a gradually increasing content of plasma hemoglobin. One should also never forget that blood is an excellent culture media; even under the best aseptic precautions, stored blood after two to four weeks may show appreciable if not large quantities of bacteria.

The value of stored whole blood is thus subject to several limitations. The red cells become increasingly more fragile and when introduced into the recipient's circulation remain a relatively short time before hemolysis occurs. This is particularly true of blood which has been stored for more than two weeks. Such blood, when introduced in the recipient's circulation may result in quick hemoglobinuria and eventuate in death. Whereas fresh citrated blood produces very little if any increase in the urobilinogen output in the feces (the best index of blood destruction), Wasserman, Volterra, and Rosenthal<sup>25</sup> showed that five-day-old blood resulted in an appreciable increase in pigment excretion and that blood older than ten days resulted in a very great output of urobilinogen. These authors, therefore advise against the use in anemia of blood stored for more than seven days. Since in addition the leukocytes and platelets become quickly reduced and the various factors concerned with coagulation of blood are appreciably diminished, it must be concluded that bank blood is of little use in the treatment of any of the so-called blood dyscrasias. It is the author's practice not to use for such conditions as severe anemia, leukopenia, thrombopenia, or the hemorrhagic

diseases any blood which has been preserved for more than 24 hours. The chief indication for bank blood must, therefore, be under conditions of emergency—as in severe hemorrhage or shock. Even here, because of the initial hemoconcentration which goes with shock, there may be some question about introducing more red cells (see below under Plasma). Probably the greatest value of whole bank blood is in the preparation of plasma; it is, moreover, a great comfort to “have in the bank” a number of bottles of already typed relatively fresh whole citrated blood ready to use at a moment’s notice.

**The Red Cells from Bank Blood—**The rapid development in the use of plasma resulted in almost complete ignoring of the mass of red cells, which were almost routinely discarded. However, many observers remarked on this great waste in a valuable by-product and in recent publications suggestions for its use have been made. The British workers MacQuaide and Mollison, and Williams and Davie used the red cells for treatment of anemia. Bagdasarov,<sup>1</sup> the director of the Russian Central Blood Transfusion Institute, reported (1942) that the red cell mass was best preserved at 4° to 6° C. with a solution containing magnesium sulfate, potassium chloride, and sodium chloride; no marked change in red cells occurred up to 12 days. The red cells were found of great value in cases of severe anemia following blood loss. L. Watson<sup>26</sup> (1943) pointed out that by the use of a thick red cell suspension one could rapidly increase the oxygen-carrying capacity of the blood with a minimum of introduced solution. This was particularly useful in ambulatory individuals and in certain cardiacs with anemia. Alt<sup>27</sup> (1943) stated that the main value of red cell transfusions is to increase the erythrocyte count in pa-

tients with anemia, particularly following severe hemorrhage. Other suggested uses are in patients with severe iron deficiency and in progressive “refractory” anemia—*i. e.*, in cases with bone-marrow disease due to aplasia, leukemia, tumors, etc. Because red cells in suspension may be given in concentrated form, larger numbers of red cells can be given at one time and more frequently than with the use of whole blood. Litwins<sup>28</sup> has suggested the use of Group O red cells admixed with pooled plasma to form a completely universal O blood, *i. e.*, one containing no agglutinogens and more or less completely neutralized agglutinins.

A new use for preserved red cells—the promotion of normal healing—was suggested by Moorhead and Unger.<sup>29</sup> T. H. Seldon and H. H. Young<sup>30</sup> state that such red cells either from a single or from different blood groups, when mixed together and stored in a refrigerator for days or weeks, form a gelatinouslike mass which may be used as a dressing material for wounds, burns, ulcers, and chronic infections. This was found of distinct value in the promotion of growth of vascular and connective tissue in the injured surfaces. Because of the difficulty of keeping the semiliquid red cell material in contact with the wound, Seldon and Young dried the gelatinous mass and used it as a fine sterile dusting powder applied directly to a wound surface. Infected wounds, poorly healing postoperative abdominal wounds, certain proctologic cases, varicose and other ulcers of the leg, and amputation stumps have been successfully treated. The method seems to offer distinct possibilities in the treatment of healing wounds.

Because of these two developments, the formerly discarded red cell by-products of the blood bank are now of distinct value: in the treatment of se-

vere anemia, particularly when the regenerative capacity of the bone-marrow is impaired, and in the promotion of better wound healing.

### Blood Substitutes

Under the impetus of the present world struggle, the use of blood substitutes has developed to an enormous degree; the most important of these—plasma—has already resulted in an incalculable saving of life. The relatively low ratio of deaths to wounded in most American casualty lists is due chiefly to two factors: *plasma* and the *sulfonamide* drugs.

Blood substitutes have their greatest value in shock, in which the principal feature appears to be a great loss of circulating blood plasma, with its resultant effects on hemodynamics. These have been thoroughly studied and described by Moon. The great diminution in plasma and total volume calls for a substance which can be quickly and safely administered and will remain within the circulation. Although whole blood fulfills these criteria, it possesses two distinct disadvantages: (1) It requires time-consuming grouping and cross-matching, with consequent discarding of various prospective donors, and (2) it adds to the hemoconcentration which is already present as a result of the loss of plasma from the general circulation. As Heyl and collaborators<sup>31</sup> have stated, a satisfactory blood substitute must possess a sufficiently large molecule to manifest colloidal properties and not be readily lost from the circulation; it must be isotonic, nonantigenic, and possess a certain degree of viscosity. Human plasma, human serum, and solutions of human albumin conform most closely to these specifications. Of these, plasma is at the present time preeminent.

**Plasma**—The use of dry plasma originated in this country as an offshoot of the cryochem or lyophile process for the preservation of sera, microorganisms, and other substances.<sup>32</sup> Liquid plasma as "a new method of blood transfusion" was first described by Elliott and his collaborators,<sup>33</sup> and by Strumia and co-workers.<sup>34</sup> Levinson and Cronheim showed that the pooling of the plasmas or sera of the several blood groups resulted in the suppression of isoagglutinin titer. The development of plasma therapy in shock has been an outstanding contribution by the medical profession of this country; England and more recently Russia have taken it up. In Germany, chief reliance has apparently been placed upon various more or less physiologic colloidal substitutes for blood.

Three types of plasma are routinely in use: liquid, frozen, and dry.

**Liquid Plasma**—This is the most readily obtained and easily handled of the blood substitutes. It may be obtained as a by-product of the (whole) blood bank, after one to two weeks of storage; or by the quick centrifugation of fresh citrated blood drawn expressly for the purpose. The numerous methods and precautions entailed have been carefully described by many authors. The preparation of liquid plasma can be readily carried out in small hospital units, requiring only (a) special flasks and needles for bleeding, pooling, and storing the plasma; (b) a good refrigerator; and (c) a large centrifuge. (The latter is not completely essential, since a fairly good yield can be obtained by sedimentation without centrifugation.)

Liquid plasma *when prepared under completely aseptic precautions* has been stored at room temperature for a year and a half or longer.<sup>35</sup> During this time, it loses none of its protein or colloidal osmotic value, but there is a rapid

loss of antihemorrhagic factors such as prothrombin and of complement. Newhouser and Lozner state:<sup>35</sup> "The permissible temperature range of preservation probably lies between 15 and 30° C. (59 and 86° F.). Below this range excessive fibrin precipitation may occur, and above this range protein denaturation occurs rapidly."

The chief advantage of pooled liquid plasma is its ready availability. It may be taken off a shelf and without further testing, reconstituting, or other steps be given immediately to an individual in shock. The intravenous set should contain a suitable filter to hold back particles of fibrin. The chief disadvantage of liquid plasma is that it is an excellent culture medium for the growth of bacteria; unless plasma is therefore scrupulously prepared, preserved, and tested for sterility, it may well become infected.

The use of liquid plasma is indicated in shock: traumatic, burn, hemorrhagic, hemolytic, etc., and in conditions of hypoproteinemia. It results in a quick increase in plasma and total volume with consequent improvement in hemodynamics. It may be given in so-called units of 250 cc. each; the tendency recently has been to give larger doses than one unit. Thus, 500 to 1000 cc. may be given without danger, although due consideration should be given to the relatively large amounts of sodium and citrate which are introduced. A caution against the too liberal use of citrated blood was recently voiced.<sup>36</sup> Citrate may be quite toxic, although the toxicity depends to some extent on the rate of injection. Five Gm. of citrate given intravenously may be considered as a safe maximum, since 15 Gm. have been shown to be fatal. [Since 50 cc. of a 2.5 per cent solution (1.2 Gm.) are customarily used for 1 unit of plasma, this

indicates that more than 4 units of plasma or 1000 cc. should not be used.] A citrate reaction,<sup>37</sup> which may result in tetany due to the binding of calcium, is characterized by the development of a positive Chvostek sign, a general tingling sensation, dilatation of the pupils, and finally actual clonic twitching. The reaction can be quickly terminated by the intravenous injection of calcium chloride or gluconate.

Previous controversy as to the relative merits of plasma and serum has gradually been resolved in favor of the former. Many thousands of transfusions with liquid plasma have been given with only occasional reactions, no greater than are seen with any form of intravenous therapy. Urticarial reactions occasionally occur. Hemolytic reactions may theoretically be due to the retention of a fairly high titer of agglutinins in some pooled plasmas. This might occur for example if all the blood pooled from eight donors were Group O (anti-A and anti-B agglutinins) or six of the eight were Group O with two A's, etc. Actually this situation rarely, if ever, occurs. The administration of badly infected plasma may, of course, be followed by septicemia, which may be fatal. By and large, therefore, pooled liquid plasma is readily prepared and quickly given and is therefore suitable for emergency use in community hospitals and in military establishments in temperate zones. It has been shipped across the country and used with success thousands of miles from the original collection point.

**Frozen Plasma**—Liquid plasma may be preserved in the frozen state in special refrigerators which maintain a constant temperature of —15 to —20° C. Under such conditions, there is indefinite retention of the various thermolabile constituents of the plasma. Reconstitution from the frozen state requires about 30

minutes at a temperature of 37° C. (the bottle being placed in a water bath, not an incubator). According to Newhouser and Lozner,<sup>35</sup> best results in thawing are obtained by this method, followed by maintenance for 2 to 3 weeks at room temperature. Quick thawing may be followed by a very cloudy-looking plasma.

The chief advantages of frozen plasma lie (a) in the preservation of sterility and (b) in the preservation of immune bodies and antihemorrhagic and other factors. The sterility factor alone has been emphasized as of greatest importance. Disadvantages of freezing lie (a) in the use of a special rather expensive freezing unit; (b) the occasional breakdown of current or apparatus with consequent thawing; (c) the necessity for slow reconstitution (thawing) making it imperative to wait at least 30 minutes, sometimes a long time in an emergency. These disadvantages can all be obviated by appropriate measures, some of which are covered by Newhouser and Lozner.<sup>35</sup> Indications for frozen plasma are identical with those of liquid plasma, with the added value that prothrombin, thromboplastin, complement are preserved in high content (from fresh plasma) and can therefore be used in suitable cases.

**Dried Plasma**—Liquid plasma may be dried from the frozen state in vacuo. Several methods of drying have been used: Lyophilization (Flosdorf and Mudd), the cryochem process (Flosdorf and Mudd), the cryochem process (Flosdorf and Mudd), the Adtevac process (Hill and Pfeiffer), etc. Using these methods, about 15 Gm. of dry flaky yellowish material are obtained from 500 cc. of whole blood (250 cc. of plasma). This material can be quickly reconstituted by the addition of pyrogen-free distilled water and given either from

the inverted original container or in a large syringe.

Dried plasma contains in unaltered form the various thermolabile globulin constituents of the previously liquid plasma, and what is more preserves them for many months without appreciable loss of activity. It has a wide range of safety with regard to temperature and bacterial contamination. However, it should not be allowed to freeze nor to stand for any length of time above 55° C. The unusual value of dried plasma in shock and cerebral accidents was quickly recognized: it could be reconstituted in relatively small amounts of fluid, thus obtaining a hypertonic material which would (a) draw unusual amounts of plasma into the circulation and (b) simultaneously "dehydrate" certain swollen tissues such as an edematous brain. The use of 2 times, 4 times, and 5 times concentrated plasma has been advocated as a routine measure by various investigators. With twice concentrated plasma, 250 cc. of water can be used to reconstitute the dried material obtained from 500 cc. of plasma. This is probably more effective in shock than isotonic plasma and furthermore adds to the circulation at once a "respectable" amount of protein. Four and 5 times concentrated plasma possesses the diluting function in even greater fashion than the twice concentrated material. Erf and Jones<sup>38</sup> dissolve the dry material obtained from 500 cc. of whole blood in 60 cc. of water which is then given by syringe rather than by gravity, as is customary when amounts over 50 or 60 cc. are used. They claim this is a far quicker and more readily available method, especially for use on the battlefield, than the gravity-tubing-filter method. Heyl and collaborators<sup>31</sup> state that the viscosity of concentrated plasma because of the presence of the globulins

is much greater than that of concentrated albumin (cf. below). The total osmotic pressure is furthermore greater because of the presence of concentrated electrolytes; however, the colloid osmotic pressure is less than that of concentrated albumin solutions.

Thus, dried plasma has many advantages: its availability at almost any temperature, its elasticity with reference to the amount of solution which need be added—thus allowing complete control of the degree of desired colloid osmotic pressure, its retention of sterility under almost any conditions. Possible disadvantages are its use in too highly concentrated form: here if the individual is dehydrated, there may be further drying of various tissues while the blood volume is becoming increased. Furthermore, in an individual with myocardial involvement, the rapid increase in blood volume may prove embarrassing to the circulation.

Dried plasma has its greatest usefulness in shock and related states. It is of value in other conditions as well: in hypoproteinemia, especially with edema, to add protein; in certain conditions of local edema as in the brain and the extremities—when other methods of therapy have failed; in chronic or acute nephritis as a diuretic, even in the absence of hypoproteinemia; in severe hepatitis, particularly in the presence of a reduced blood protein and ascites. It would probably be even more widely (and unwisely?) used in civilian practice than it is at present were it less expensive. Sufficient dried plasma for the military services has fortunately been supplied by volunteer donors, with the invaluable assistance of the Red Cross and of various pharmaceutical houses.

**Purified Protein of Human and Animal Plasmas—*Human Albumin*—**Plasma is a very complex solution. It

not only contains proteins which are essential for its own stay in the circulation, but has all the various hormones, enzymes, metabolites, etc., which are in process of transportation from one tissue to the others. It has been customary to divide the plasma proteins roughly into two fractions: albumin and globulin. The albumin fraction is relatively pure, but the globulin fraction is composed of a large number of substances which differ greatly from one another with respect to their chemical structure and their function.<sup>39</sup> Although great strides have been made in studying these complex proteins, it is probably safe to say that thus far only the surface has been scratched. Two of the important tools in studying the plasma proteins are the Tiselius apparatus for the observation of electrophoretic mobilities and the ultracentrifuge.

The task of purification and fractionation of human and animal plasmas for military use has been undertaken by the Department of Physical Chemistry at the Harvard Medical School, under the direction of Professor E. J. Cohn. Disregarding respiratory, hormonal, and enzymatic proteins, the plasma proteins may be divided (Cohn)<sup>39</sup> into those concerned (1) with clotting of the blood; (2) with complement; (3) with immune processes including antibody and antitoxin; and (4) with water and electrolyte balance. Among those which have thus far been identified are fibrinogen and prothrombin and the “mid-piece” and the “end-piece” of complement. The bulk of the various globulins comprising the globulin fraction of plasma has thus far not been separated in pure form; they have been characterized either as endoglobulins or pseudoglobulins or in terms of their electrophoretic mobilities (alpha, beta, and gamma globulins). In general, the globulins have a very high molecular



weight and on that account exert a smaller osmotic pressure than the smaller molecules of albumin. The separation in relatively pure form of the more simple albumin fraction from the complex globulins has been effectively accomplished by Cohn and his collaborators.

The albumin thus prepared and freed from the more labile and more readily denatured fibrinogen and globulins, is readily soluble in water, yielding clear solutions even at concentrations containing as much as 70 per cent of albumin by volume. Even in concentrated form, albumin solutions have a lower viscosity than plasma, interact only slightly with other proteins and salts, and "stand up" under conditions of extreme heat and cold.<sup>35</sup> Furthermore, they exert a much greater colloid osmotic pressure than whole plasma. For these reasons and because of their immediate availability for intravenous injection, albumin solutions have proved extremely useful in the treatment of wound shock. The standard Army-Navy package of concentrated human albumin solutions consists of 25 Gm. of albumin in 100 cc. of buffered salt solution, supplied in a large ampule ready for instant injection by gravity through an ordinary No. 19 or No. 20 needle.

Heyl, Gibson, and Janeway<sup>31</sup> have calculated that each gram of albumin injected intravenously would be expected to add by osmotic pull 18 cc. of fluid to the circulation. These calculations, when subjected to actual experimentation in the human subject, were found to be surprisingly accurate; thus the actual increment in plasma volume varied from 13.2 to 24 cc. in all experiments, with an average value of 17.4 cc. The use of 25 Gm. of albumin is thus approximately equivalent to the administration of 450 cc. of normal circulating plasma

or 500 cc. of citrated plasma, as usually prepared.

Thus, a concentrated solution of purified albumin possesses many advantages. Certain disadvantages must also be assessed. Because of its very great osmotic pull, there is a real danger of dehydrating vital tissues, especially in individuals like soldiers, who have been exposed to many hours of struggle under conditions of extreme heat and thirst. For this reason, the use of albumin solutions should probably be restricted to hydrated or only slightly dehydrated individuals. Another disadvantage of albumin solution is of course its lack of globulin substances and thus of enzymes, blood coagulating materials, and antibodies. The administration of several injections of albumin solution has furthermore been found to result in a modification of the albumin-globulin pattern of the plasma with possible effects on immune reactions.<sup>40</sup>

Indications for albumin solution are thus relatively few, and depend entirely on its great colloidal osmotic pull. It is thus useful in shock and in conditions associated with hypoproteinemia and edema. As yet, it is not available for civilian use; even if it were, its cost would probably render its use almost prohibitive. Partly for this reason and because of ready availability, the preparation of albumin from animal sources has been given much thought.

**Bovine Albumin**—Cohn and collaborators<sup>39</sup> have shown that human and bovine albumin present remarkably similar molecular patterns from a physicochemical point of view. Both by means of the ultracentrifuge and the Tiselius electrophoretic apparatus, the two albumins are to all intents and purposes indistinguishable. The chief difficulty is, however, not the physicochemical one but rather the immunological reaction.

This probably develops because of slight contamination of albumin with globulin. The matter of development of sensitivity to a heterologous material is of great importance and has been studied by Janeway<sup>41</sup> and by Heyl, Gibson, and Janeway.<sup>31</sup> The latter authors came to the following conclusion: "No statement regarding the safety for intravenous use of crystallized bovine serum albumin of low globulin content can be made until more extensive clinical tests have been completed in order to determine to what extent and under what circumstances it will be safe to use a protein of animal origin for therapy in man."

**Other Substitutes<sup>3</sup>**—Numerous materials other than those derived from blood have been suggested as substitutes for blood or plasma. Most of them have for various reasons proved unsatisfactory, but search for a practical, inexpensive material is still going on. As noted above, such a substance must have a sufficiently large molecule to manifest colloidal properties and not be readily lost from the circulation. It must also have a viscosity fairly comparable to that of the blood, be isotonic and nonantigenic.

**Acacia**—The intravenous administration of acacia for the treatment of wound shock was introduced by Bayliss in 1916. It proved to have only limited value, chiefly because of fairly frequent severe reactions which took place. Acacia is made up of particles of variable size which exert (in 6 per cent solution) a colloidal osmotic pressure approximately equivalent to that of serum protein. Since the particles of acacia do not freely permeate the capillary wall, their pressure within the circulation results in the attraction of extracellular fluid to the plasma and in a consequent increase in the circulating plasma volume.

The use of acacia solutions in shock has naturally become greatly diminished because of the rapid developments in the field of transfusion of whole blood, plasma, etc. It is, however, available in ampules of 100 cc. of a sterile 30 per cent solution either in distilled water or with 4.5 per cent sodium chloride. For use in shock, the latter solution, diluted four times with sterile distilled water is used, thus giving 500 cc. of a 6 per cent acacia solution in 0.9 per cent NaCl solution.

Acacia, being made up of small colloidal particles, attracts about it large masses of platelets. These frequently form thrombi which lodge in lungs or other viscera. Experimental studies (unpublished) which the author made several years ago showed an extreme drop in platelet count and the development of thrombi following the rapid injection of acacia suspensions. For this reason it is important to inject the solution slowly.

The judicious use of repeated daily injections of acacia solution has in recent years proved of distinct value in the treatment of refractory nephrotic edema (Landis, Goudsint and Binger). Following courses of acacia, weight reductions of 11 Gm. of edemic fluid have been reported. Diuresis usually begins on the third or fourth day of therapy. The continued presence of acacia in the blood for long periods of time has been shown by Jackson and Frayser to cause a depression in the formation of serum protein. The use of acacia will probably be drastically curtailed with the great increase in the administration of blood and its derivatives.

It has certain disadvantages not already mentioned, *i. e.*, to a certain extent it is antigenic; it may cause liver damage—probably through small thromboses; it may depress greatly the plasma proteins, particularly fibrinogen; and the

bleeding time may be greatly increased—probably because of a reduction in platelets.

**Casein Digests**—The experiments of Madden and his co-workers<sup>42</sup> in the famous Whipple dog colony at the University of Rochester have shown that certain digests of casein given by vein or subcutaneously are promptly used by the hypoproteinemic dog to produce needed plasma proteins. In a long series of experiments it was found that normal dog plasma given by vein to the protein fasting dog could supply all the protein requirements. Although casein digest is much less effective than plasma, it was as effective intravenously as liver protein or casein digest given by mouth. Casein digest "L" (Lilly and Co.) was prepared by papain digestion of commercial casein, the final material being readily soluble, golden-yellow, granular, and having an approximate protein content of 78 per cent. It was given in 5 per cent solution. Madden and co-workers suggest that since casein digests given intravenously or subcutaneously are as effective as protein by mouth in building new plasma protein, they can be used to supplement plasma injections or even replace them when the acute emergency of shock is over. Since the digests are obtainable in unlimited amounts, are easily sterilized, completely nontoxic, and are readily stored in concentrated form, they should find increasing clinical use in long drawn-out illnesses, following intestinal operations, in ulcerative colitis, etc.

**Miscellaneous Substances — Gelatin**—The use of gelatin as a readily obtainable material having colloid osmotic properties was studied by Kleinberg and collaborators<sup>43</sup> at Princeton. The administration of a 5 per cent solution of gelatin in normal salt solution effectively prevented the development of traumatic

shock in dogs, and was therapeutically effective in at least 50 per cent of shocked animals. Parkins and Lockwood<sup>44</sup> found that gelatin in a 6 per cent solution in normal saline was osmotically active in dogs, but that drastic fall in plasma proteins took place, together with an increase in the coagulation time and possible disturbances in the liver function. E. T. Waters (Toronto) found that Eastman's purified gelatin, made from green stock calf skin, and given to dogs in a 7 per cent solution was osmotically effective in hemorrhage and shock and caused no significant changes in the coagulation time. It was found that the gelatin remained in the circulation for at least three days and was relatively innocuous. It should be noted that since gelatin is derived from an animal source, it may have definite antigenic qualities.

**Isinglass**—Taylor and Waters reported that a solution of isinglass prepared from the swimming bladders of fish possessed a number of the essential properties of a blood substitute. The original hope that a uniform product of sufficiently high balance would be obtained from the swimming bladders was, however, not supported by later experimentation (cf. Waters).

**Synthetic Colloids**—The Germans seem to have done very little with blood serum or plasma, either human or bovine, but apparently place greatest reliance on artificially prepared colloids. Thus, Hecht and Weese<sup>45</sup> describe a synthetic colloid, polyvinyl pyrrolidone ("Kollidan") with a mean molecular weight of 25,000, well-defined colloid osmotic properties, well tolerated, and remaining at least two days in the circulation.

The Russians, who among other things have excelled in the quick evacuation and emergency treatment of their wounded, have—as noted above—used whole blood,

plasma, and red cell infusions with excellent results. In addition, Bagdasarov<sup>1</sup> discusses "physiologically balanced solutions," the exact composition of which is not described, but which contain a little plasma, some alcohol and glucose, and probably other materials. It is said that these solutions "mainly reinforce the vital processes" and are used in those wounded who are suffering from "disturbed hemodynamics" not associated with severe blood loss and in septic cases. Also with the idea of improving the "vital processes" of the wounded, the frost-bitten, and the infected has been the development by Bogolomets<sup>46</sup> and his co-workers of the Soviet Union of "anti-reticular cytotoxic serum" as reported in the December, 1943, issue of the *American Review of Soviet Medicine*. This serum is stated to be a powerful specific factor influencing the physiologic system of the widespread connective tissue and therefore useful in many diverse conditions, particularly in military medicine.

**Sites of Administration**—The preferred site of administration of whole blood, plasma, and the various blood substitutes is naturally in the various large veins which are usually readily found in the antecubital fossae. In extreme shock and in extensive burns, these veins may either be collapsed or inaccessible. It is well, therefore, in emergencies to have in mind the possibility of administering these substances in other than the basilic veins. The *femoral vein* is not customarily thought of in this regard, but its use might well be increased. The vein is extremely large and is situated just medial to the femoral artery, which is readily palpated in the inguinal region. With a little practice puncture of the vein is readily performed. Administration of plasma by this route was found extremely useful by

the Boston City Hospital group during the Cocoanut Grove fire disaster in 1942.

The infusion of blood and other fluids by way of the *sternal marrow* was suggested by Tocantins in 1940 and has gradually assumed increasing use. Tocantins demonstrated by careful injection experiments in cadavers, and later by clinical studies in animals and humans, that substances injected into the marrow cavity are taken up immediately into the venous circulation apparently unchanged. In adults, the marrow cavity of the sternum is readily entered by the introduction of a sternal puncture needle (an abbreviated stiff lumbar puncture needle will do) through the skin and subcutaneous tissue and then through the anterior lamella of the sternum. The procedure which is done under novocaine anesthesia is a simple one and is readily learned. A sensation of "give" is felt when the needle enters the marrow cavity. The needle stilet is then withdrawn and a small amount of marrow aspirated. An adapter may now be attached to the needle and attached to rubber tubing and a gravity device, or the blood or fluid may be introduced under positive pressure by means of a syringe. If the injection of more than 50 cc. is contemplated, it is wise to use a two-way stopcock and thus avoid removing the syringe from the needle for each 50 cc. As Tocantins states, rapid injection (over 20 cc. per minute) may be accompanied by a sense of pressure or grinding pain similar to that of angina pectoris; this quickly disappears at the termination of injection. However, it is rarely necessary, or even advisable, to inject fluids at such a rapid rate. The use of the intrasternal route is particularly applicable to military medicine and a number of reports from military establishments in which its use is favorably commented upon have appeared.<sup>47, 48</sup>

In one such report, the sternal puncture needle was allowed to remain *in situ* for three to four days with occasional cleaning; 14,000 cc. of blood and fluid were given with no untoward effects.

The marrow may also be used for the introduction of fluids and blood into the infant's circulation. Tocantins' studies have shown that in the newborn and in early infancy, the marrow cavity either above or below the knees is best utilized. In older children (ages two to four) the midtibia may be better. Above the age of four, the sternal cavity may be fairly well developed and thus available for injection.

The administration of fluids and blood *in infancy* is almost a speciality in itself, apparently reaching its highest development in internes and residents of children's hospitals and services. Positive pressure is required for the administration of fluids in the *scalp veins* of young infants. The *external jugular veins* are fairly large and usually readily entered if the infant is held tightly bundled and the head and neck kept in extrusion. The *veins above the ankle* may require "cut-downs." If none of these vessels can be entered, recourse may be had to one of the *bone-marrow cavities*, as noted above.

### Dosage

**Whole Blood, Fresh or Bank**—A transfusion of blood once having been decided upon for good and sufficient reasons, it is imperative to give a sufficient amount. The often glibly expressed opinion that "small transfusions" are of value in this or that condition is based upon no physiological grounds that the author has been able to discover. A transfusion of 500 cc. of blood may really be considered to be a "small" transfusion, since it usually represents an addition of only about 10 per cent to the patient's blood volume. In certain cases,

as in severe or continued hemorrhage, 1000 to 1500 cc. of blood may be necessary. Blood by continuous intravenous drip, *in 5000 cc. amounts daily*, has been given for bleeding peptic ulcer without untoward reaction. Thus, if a transfusion is really necessary, it should be given in sufficient quantity, and not as a "token" administration. Five hundred cc. is a minimum dosage for an adult; infants and young children take 100 to 250 cc. depending upon their body weight. Individuals with an impaired or potentially impaired circulation should receive blood very slowly, if at all.

Red cell transfusions have been given in large amounts. It has been customary to give the red cells in one dose derived from 1000 cc. of blood. This is in keeping with the idea that if the transfusion is required, it should be given in sufficient amount.

**Plasma—Liquid Plasma**—This is usually put up in "units" of 250 cc. derived from 500 cc. of blood, and has recently been given routinely in greater amounts than when first introduced. Thus, Newhouser and Lozner<sup>35</sup> state that the majority of (military) patients are now receiving an initial dosage approximating 500 cc., especially in the war zones. They further state that in shock due to trauma and burns, it is essential to give an adequate amount early, preferably before the full symptoms of shock have appeared. The amount of blood derivative required is directly related to the elapsed time after injury. Since death may occur due to insufficient dosage, it is frequently advisable to use from 500 to 1000 cc.

In burns, a rough rule for estimating the first day's dosage is to administer 100 cc. of plasma for each 1 per cent of body surface burned, up to a maximum of 4000 to 5000 cc. Estimation of the area involved is made by reference to Berkow's chart (see Newhouser and

Lozner<sup>35</sup>), or from the knowledge that the palmar surface of the hand represents approximately 1 per cent of the total body surface. Another method for estimating dosage is by means of the hematocrit, which roughly tests the degree of hemoconcentration. Harkins has advised the use of 100 cc. of plasma for every point the hematocrit is above 45. Thus for hematocrit 50, 500 cc. should be given. These concepts were tested at the Boston City Hospital following the Cocoanut Grove disaster by Dr. Charles C. Lund, Dr. F. H. L. Taylor, and co-workers,<sup>49</sup> and found helpful.

Strumia and McGraw<sup>34</sup> prefer to speak of plasma in terms of grams of plasma proteins; 35 to 36 Gm. are ordinarily obtained from 500 cc. of undiluted plasma. In cases of shock with or without hemorrhage, this is the customary initial dose, although two or three times this quantity may be used. Burns require perhaps more plasma because of the continued loss of proteins from the burned area. Further special dosage schedules for plasma are given by Strumia and McGraw<sup>34</sup> for hypoproteinemia, hepatitis, severe infections, hypoprothrombinemia, etc. It is always imperative to give enough.

**Dry Plasma**—As noted above, dry plasma may be reconstituted in a variety of amounts of solution, thus giving varying degrees of hypertonicity. A good case has been presented for the use in shock of at least twice concentrated plasma; four and five fold concentrations are certainly convenient to use since they may be given by syringe. The Army and Navy have not as yet recommended the higher concentrations.

**Albumin**—Since 25 Gm. of albumin in 100 cc. of solution is osmotically equivalent to 500 cc. of plasma, either 25 or 50 Gm. of material may be initially used. The later dosage is probably too

high for a badly dehydrated individual. Continued administration of albumin is probably undesirable.

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## DISEASES OF THE KIDNEY

FRANCIS D. MURPHY, M.D.

## Renal Function

The outstanding contribution of the year in the field of renal disorders is the comprehensive picture of renal function in man given by Homer Smith<sup>1</sup> in his lecture, "Newer Methods of Study of Renal Function in Man." He takes up a review of the basic principles of renal function and discusses the prominent theories regarding tubular and glomerular activity. The rôle of the tubular apparatus and its excretory functions are given in detail. The newer methods, which have become almost standard procedures in study of the kidney are described. This paper makes up a chapter in the author's book, "Lectures on the Kidney."

The effect of extrarenal conditions on kidney function has been given considerable attention this year. Post,<sup>2</sup> in a report on the progress on problems of Bright's disease, points out the influence of endocrine disorders, diet and vitamin

deficiencies, infections, and allergy on the kidney.

Barnett, Perley and Heinbecker<sup>3</sup> state that the glandular hypophysis has a humoral influence on the kidney and that the eosinophil cells of the hypophysis are responsible for this influence. They substantiate this statement by citing the fact that in acromegaly with eosinophil cell hyperplasia or eosinophil tumor, there is often found an increase in renal function and size which may well be due to the increased secretion of the hypophysis. When the hypophysis is removed from dogs with one kidney only, renal hypertrophy does not develop, presumably since the stimulation from the glandular part of the hypophysis is gone. Heinbecker, Rolf and White<sup>4</sup> later noted that glandular hypophysis given subcutaneously to normal and hypophysectomized dogs and to dogs with a hypothalamic lesion of the sort causing diabetes in-



insipidus and obesity caused an increase in the excretion of diodrast and inulin, and in the maximum excretion of diodrast at high plasma levels. This same effect is brought about to a lesser degree by thyroid extract. These observations caused them to believe that it is the anterior lobe of the hypophysis that has a trophic influence on the kidney. The polyuria of diabetes insipidus in dogs and cats may be diminished by keeping the chloride intake constant and reducing the nitrogen intake, and it may be increased by increasing the nitrogen content of the diet. Reduction of the polyuria of diabetes insipidus is best brought about by restriction of both the nitrogen and sodium chloride intake.<sup>5</sup> MacKay and Sherrill<sup>6</sup> found that there is a direct relation between renal function and the basal metabolic rate, which is more constant when basal metabolism is low. Polyuria resembling that of diabetes insipidus may be produced in normal dogs by injection of 2.5 mg. to 10 mg. of desoxycorticosterone acetate daily, and the syndrome of diabetes insipidus is aggravated in this way.<sup>7</sup>

The part of the renal innervation in renal tubular function was studied by Maluf,<sup>8</sup> who found that the nerve supply to the kidney does not affect renal tubular secretion in regard to water, chloride, and phenol red. He transplanted dog kidneys to the femoral region by end to end anastomosis of the renal vessels with the femoral vessels, and exteriorized the bladder and ureteral orifices. The amount of water and chlorine resorbed per unit volume of glomerular filtrate (inulin or creatinine clearances) was the same in both the transplanted and nontransplanted kidney during both the antidiuretic and diuretic urinary flows. Since the ratio of inulin and phenol-red clearances was also practically identical for both kidneys, it was inferred that the

fraction of phenol-red outwardly secreted by the tubules of both kidneys was the same. Differences in the rate of excretion of water and various solutes by the normal and denervated kidney are felt by this investigator to be due not to differences in tubular function, but to changes of glomerular circulation.

Newburgh<sup>9</sup> emphasizes the importance of osmotic work in renal function. He feels that the implications of this requirement have not received the consideration they deserve by physiologists or clinicians. Osmotic work may be reduced in several ways, as by the control of water and sodium chloride intake, and realization of this may be important in the treatment of kidney diseases.

The effect of temperature on renal blood flow and glomerular filtration was investigated by Byfield, Telser and Keeton,<sup>10</sup> who worked with patients in comfortable and hot environmental conditions. They discovered that the inulin clearance was not affected. The renal plasma flow was unchanged in patients with well maintained inulin clearance, but slightly decreased in those with decreased inulin clearances. In two of six cases, the diodrast maximal rate of tubular excretion increased. Subjects with lowered inulin clearances could not conserve water as well as normal subjects, as tubular absorption was diminished.

Failure of part of the kidney may cause an increase in function of the rest of the kidney, and in certain cases of diseased or destroyed kidneys, the kidney has enormous regenerative power.<sup>11</sup> Hinman<sup>12</sup> discusses the theory of renal counterbalance and disuse, and reported on studies he had done on animals in his study of this theory. He concludes that atrophy or hypertrophy and the principles relating to the potentials of functional stimulation and kidney reserve power by which these renal changes bring

about a counterbalance should be kept in mind in every clinical problem of renal repair and restoration of function.

Post,<sup>2</sup> in epitomizing the modern tests of renal function, recommends the following procedures: (1) Concentration and dilution tests of Volhard or Mosenthal or some modification; (2) Addis count of the formed elements in urine; (3) excretion rate of phenolsulfonphthalein; (4) quantitative estimations of non-protein nitrogens of the blood urea, uric acid, creatinine, and total nonprotein nitrogen; (5) urea excretion ratio of Addis and Drury and of Watanbe; (6) urea clearance. Post states that this is one of the most valuable when account is taken of the fact that the test holds best for moderate to high urine flows and that it is much lower than the glomerular filtration rate. This is probably due to the fact that urea is absorbed in the tubules. This reabsorption rate changes with the rate of urinary flow in the tubules and the plasma urea level; (7) (exogenous) creatinine filtration rate and concentration ratio devised by Rehberg. This has been criticized by some, since the filtration rate is high due to the secretion of creatinine by the tubules, and the methods for identifying and estimating creatinine are not perfectly specific; (8) inulin and diodrast clearance tests. Inulin is filtered only by the glomeruli and not secreted or absorbed by the tubules or combined with plasma protein; thus inulin clearance is an accurate indicator of glomerular function. Diodrast measures renal blood flow and tubular function. The test is rather complicated and requires a good deal of equipment, a fact which accounts for its limited use in clinical practice; (9) determination of the carbon dioxide volume per cent (or bicarbonate) and the Cl level of blood plasma, plasma sulfates and phosphates, plasma total base or sodium and the

plasma pH and sodium and chloride of the urine to evaluate the efficiency of renal control of body fluids; (10) quantitative determination of plasma proteins and possibly their fractionation and estimation of albumin and globulin, or the determination of the colloidal osmotic pressure of plasma; (11) skin absorption time for salt solution used to determine the presence of conditions leading to edema.

The chief guide in determining renal damage according to Davis<sup>13</sup> is the urea clearance test. He devised a new normographic method for its determination. In his modification of the test, urea must be given by mouth in order to put a load or stress on the kidney. All aspects of the test should be considered before making conclusions. For this Davis uses his normographic chart, which allows the clinician to determine from all available data the true urea clearance value. All mathematical formulae are eliminated. Repeated tests are needed in order to follow a case and make an accurate prognosis.

Dominguez and Pomerene<sup>14</sup> state that urea clearance in man rises continuously with diuresis at all diureses in both health and renal disease. This effect also occurs in nephrosclerosis both before and after denervation. They say that the concentration ratio of urea and urea clearance are mutually equivalent at all diureses and that if the equation for one is known, the other will also be known. Since there is a correspondence between the clearance and concentration ratio of urea, when comparing the concentration tests of renal function with urea clearance, both the specific gravity of the urine and the clearance or concentration ratio should be compared at the same urine flows. It is suggested that the clearance of other substances, as inulin

and creatinine, should also be computed according to the formula they use.

Smith, Goldring, Chasis, Ranges, and Bradley<sup>15</sup> applied saturation methods to the study of glomerular and tubular function in the human kidney. They studied particularly the possibility of intermittency of glomerular activity and tubular perfusion. Their investigation indicated that normal subjects should have few nephrons with a glomerular activity below 0.60 or above 1.5 times the mean glomerular activity for the entire kidney. In normal subjects not much tubular tissue has a perfusion below 0.66 or above 1.66 times the mean tubular perfusion for the entire kidney. The distribution of tubular perfusate and glomerular activity may be perfectly normal in the presence of long standing hypertension, and tubular perfusion tends to remain normal in those with diminished or increased glomerular activity.

In a study on the calculation of renal resistance to the blood flow, Lampert<sup>16</sup> made observations on the osmotic pressure and viscosity of the blood. He describes a method by which the serum protein of any albumin-globulin ratio can be converted easily into an osmotically equivalent concentration of serum protein of A:G ratio 2.20 by means of formula or chart.

In this connection Findley, Edwards, Clinton, and White<sup>17</sup> have devised a chart which simplifies the original technique of Smith for determining the renal blood flow and tubular excretory mass. These simplifications of complicated procedures promise to be very helpful if the information they provide is as precise as the original.

A study of the reduction of phosphatase in damaged kidneys is reported by Wilmer.<sup>18</sup> He points out that the phosphatase activity was reduced to one-sixth of normal when the death of the experi-

mental animal was due to chronic nephritis with uremia. The disturbance of excretion of potassium in renal diseases has also been given some consideration by Keith, King, and Osterberg.<sup>19</sup> A sustained increase in serum potassium is an unfavorable prognostic sign.

Modifications of the concentration tests of renal function by the use of pituitary extracts have been reported, and they deserve further trial.<sup>20, 21</sup> Estimations of kidney function are approached from another angle by observations made with the aid of intravenous urographical studies.<sup>22, 23</sup>

The significance of proteinuria is commented on by Addis.<sup>24</sup> He and his associates raised the dietary protein intake of rats and at the same time decreased the number of nephrons. The result was an increase in the rate of protein excretion proportional to the increase in protein consumption or decrease in kidney size. The effect occurred in about 40 days and was outstanding in 80 days. The experiments seemed to indicate to them "that in the rat the rate of protein excretion increases after the amount of osmotic work per gram of renal tissue or per nephron has been increased. The effect on the kidney is the same whether the increased rate at which each nephron has to excrete urea (the principal factor that determines the osmotic work it is required to do) is induced by an increase in protein consumption or by a reduction in the number of nephrons. . . . It is equivalent to saying that protein excretion can be altered by a factor that is effective with respect to the tubules, not the glomeruli. Nevertheless, we regard our interpretation as the simplest hypothesis. It seems to us preferable to assuming a change in the permeability to protein of the glomeruli of young rats in a relatively short space of time, a change for which there is no anatomical

evidence." Addis feels that these experiments are compatible with the theory that tubules reabsorb protein, and that in addition to glomerular damage, tubular damage affects the amount of protein excretion.

### Renal Diseases

This review of renal diseases will include a discussion of the recent literature on nephritis, nephrosis, and renal arteriosclerosis, as well as pyelonephritis and some of the more uncommon renal disorders, as inflammatory lesions of the kidney due to sulfonamides and other agents. The contributions to the literature in this field of work have been numerous, and while all of them cannot be reviewed, those of most practical importance will be taken up. Many articles have thus been excluded, not because of their lack of value, but because their technical nature does not render them suitable for the present purpose. From the clinical standpoint, the review by Bradley<sup>26, 188</sup> is a splendid summary of the current literature on Bright's disease. His digest of the renal therapy of nephrotic edema is especially important, and the analysis of crush syndrome and related conditions is illuminating.

**Acute Glomerulonephritis** — Acute glomerulonephritis is an acute inflammatory lesion of the glomeruli. There is no unanimity of opinion concerning its etiology, although it is considered to be due to an infectious process somewhere in the body, usually streptococcal in nature. This malady is frequently brought on by upper respiratory infections, cellulitis, and scarlet fever.<sup>27</sup> Hunner<sup>28</sup> believes that ureteral stricture may often be the cause of Bright's disease, and that any patient suspected of Bright's disease should be subjected to a thorough urological examination. Relief of ure-

teral stricture according to him may relieve the nephritis.

The basic lesion is swelling and proliferation of the endothelial cells of the glomerular capillaries and accumulation of an inflammatory exudate and leukocytes within the loops. The result is obstruction of the glomeruli, which may be attended by tubular atrophy. The pathology is not limited to the kidneys, and nephritis is now considered a part of a generalized vascular disease.

The disease process is marked by five main syndromes: (a) The urinary syndrome; (b) hypertension; (c) edema; (d) retention of nitrogenous products in the blood, and (e) uremia. These syndromes may be present singly or together. The urinary syndrome is the most important because it is always present and is the most reliable. Oliguria is often outstanding, and is probably the result of actual capillary obstruction due to proliferation of the endothelial cells of the capillaries. Specific gravity is also inclined to be high, 1.025 or above. Sometimes the output of urine is more normal in quantity and specific gravity. As a rule, a low specific gravity indicates a chronic lesion. Casts, hyaline and granular, many red blood cells, gross hematuria, and numerous pus cells are also present. Blackman and Davis<sup>29</sup> noted that in progressive renal insufficiency the gamma globulin concentration is high, whereas in normal persons and those with chronic lipid nephrosis it is low. Albuminuria is a constant feature, and is present as long as the kidney lesion persists. Bell<sup>27</sup> states that the proteinuria is due to the passage of plasma protein through the walls of the injured glomerular capillaries. Addis<sup>24</sup> suggests that proteinuria is a sign of tubular as well as glomerular damage. Edema is often present, but is a benign complication and seldom generalized in the acute

stage of nephritis. Hypertension is a more serious sign, though a moderate elevation of the blood pressure is a common finding in the acute phase. The early elevation in blood pressure is probably the result of a functional change in the renal arterioles. If the oliguria or anuria persists, nitrogen retention develops and may progress to uremia. Uremia may be either of the genuine or convulsive type. Genuine uremia is the direct result of renal insufficiency; it is due to the accumulation of toxic material in the body, and carries a bad prognosis. Convulsive uremia is not dependent on renal failure, but is distinguished by hypertension and cerebral edema with eyeground changes. Patients may recover from this type of uremia and live for long periods afterwards.

Serum lipids in patients with renal disease were studied by Peters and Man<sup>25</sup> who found that hypercholesterolemia, and elevation of neutral fat is often present. The hypercholesterolemia could not be correlated with any single feature of these diseases. The relation of cholesterol to lipid phosphorus is not deranged as a rule, and both cholesterol and lipid phosphorus levels fall when the renal disease clears, or when renal failure sets in, or during exacerbations and other complications which interfere with nutrition.

The heart is often affected adversely<sup>30</sup> in the course of acute glomerulonephritis and heart failure is a frequent cause of death in the acute stage. This heart damage may resolve completely, leaving no trace in patients who recover. Those with cardiac decompensation may have dilatation with or without hypertrophy. The severity of the nephritis, height of the blood pressure, and incidence or severity of heart complications do not correlate.

Prognosis should be guarded. The intensity of the acute attack does not influence the ultimate outcome of the disease. Severe types may clear up entirely and mild attacks may develop into chronic nephritis. It is well known that the renal lesion of acute nephritis is entirely reversible and that the patient with all the features of nephritis, both clinical and pathological, may recover rapidly and completely without any recurrence of signs and symptoms of the disease. Following the acute episode, whether it is mild, moderate, or severe, there is a period of about six weeks in which the patient appears much better, and even completely cured. However, in such cases, a more thorough study will show that a renal lesion often persists. This period when the inflammation has subsided but is not entirely healed is known as the transitional or latent period. It is important to recognize this period, as it is during this time that the nephritis becomes cured or passes on to the chronic form.

The condition of the kidney should be accurately determined, so that treatment is not relaxed before it should be. No one test has been found a reliable prognostic guide in every case, but a combination of several measures may give fairly accurate information: (1) A count of the casts and cells in the urinary sediment by the method of Addis is the greatest aid; (2) determination of the ability of the kidney to concentrate urine by Volhard's method is reliable, and progressive impairment of concentrations points to a progressive, unhealed lesion; (3) the blood urea clearance test is helpful. When the urea clearance is low at the beginning and improves in time, the outlook for the patient is good, but if it continues to drop in percentage, the outlook is poor; (4) an unresponsive anemia is a serious sign; (5) estimations

of plasma protein are important prognostically. Even though the plasma albumin does not drop to the critical level of 2 Gm. per 100 cc., a lowered plasma albumin content, for example, 3 Gm. per 100 cc., and a value for total protein of less than 5 Gm. per 100 cc. indicates an unfavorable prognosis; (6) nearly always the determination of the erythrocyte sedimentation rate is helpful. A rapid rate points to an unhealed lesion becoming progressive, while a slowing down of the sedimentation rate points to healing of the inflammation. A normal sedimentation rate indicates that the lesion is either healed or nearly healed.

Bell<sup>27</sup> finds that about one-half of persons with acute glomerulonephritis recover completely, a small percentage die of uremia in the acute stage, and many pass over into the subacute, latent chronic, or active chronic stages. Murphy and Peters found that of 205 patients, 41 per cent were completely healed, and 43.5 per cent still showed latent or chronic nephritis. Twelve and six-tenths per cent died in the acute stage.

The general principle in the treatment of renal disease is described by Leiter<sup>31</sup> as an attempt "to correct dysfunction or to adjust the patient to residual function. In his natural desire to 'treat the kidneys,' the physician must not lose sight of the fact that the patient as a whole is more important than his edema, his blood chemistry, or his blood pressure." Thorn<sup>32</sup> feels that treatment of renal insufficiency might be simplified by basing therapy on a consideration of physiologic principles rather than on pathology. Since the etiology of nephritis is vague, and the disease may present so many different aspects, treatment cannot be standardized, and the various syndromes must be treated as they occur. For this a knowledge of the chemi-

cal and physiologic changes are necessary. Accurate diagnosis is the basis for successful treatment, and this in turn depends on a combination of skillful clinical observation and the use of the standard renal function tests. The patient must be shielded from infections as much as possible, and the kidneys protected when infection actually sets in. Complete *rest*, *alkalinization*, and *regulation of food intake* are the chief safeguards in this phase.

The patient should be kept in bed until all signs of renal inflammation have passed over. This means more than keeping the patient in bed while hypertension, edema, and hematuria exist. The patient must remain in bed as long as the microscopic examination of the urine shows red cells, casts, and albumin, and until the sedimentation rate becomes normal. The use of the other tests mentioned will also help in determining whether or not the patient can get up. It is generally well to insist on four months of modified bed rest. If the kidney has not cleared up by this time, the condition is probably chronic and further rest will do no good.

When foci of infection are present, they should be removed so as to lessen the chances of future exacerbations. It is best to delay until the acute stage is over, as if surgery is undertaken too early, the process may spread. Associated infections may be controlled with *sulfonamides*. Leiter recommends *sulfanilamide*, as it is less likely to precipitate in the urinary tract. It is interesting to note that the nephritis itself may be benefited by sulfonamide therapy. Murphy and Wood<sup>33</sup> observed good results in three cases of nephritis given sulfanilamide, sulfadiazine, and sulfathiazole, respectively. In renal insufficiency, of course, extreme care must be taken to avoid complications.

The diet should contain little protein, salt, and water as long as the kidney cannot excrete them or their waste products. However, enough of the necessary food elements must be included to insure proper nourishment to the patient. It has been said that rigid restriction of salt, proteins, and fluids, except for 400 to 600 cc. of fruit juices, is advisable for three or four days, but that after this the quantity of food and fluid can be increased as required. When body proteins, especially albumin, are reduced, it is wise to give more protein to make up the deficiency. Albumin is particularly beneficial in such cases.

Treatment of the oliguria may be difficult or easy.<sup>31</sup> If it is due to functional renal insufficiency secondary to dehydration, *parenteral fluids* and *electrolytes* are all that is necessary, unless the circulation has been damaged by prolonged shock. Obstruction of the urinary tract may be a cause of the oliguria. This should be constantly kept in mind and adequately treated when present. *Mercurial diuretics* are to be avoided unless the oliguria is obviously of cardiac origin. If dehydration is present, hypertonic glucose may result in direct renal tubular damage. It may be given to furnish calories in a patient who is vomiting excessively, but the fluid and salt requirements are more important. Determinations of serum chloride and bicarbonate will help in determining of what composition the fluid should be.

When oliguria is due directly to renal failure, fluid therapy may result in overloading the circulatory system, and thus lead to pulmonary edema, and encephalopathy. Leiter emphasizes the fact that the more severe the oliguria in acute nephritis, the more rigid should be the restriction of salt and fluids. *Carbohydrates* in the form of jellies, fruit juices, starches, and so forth, may be given for

nourishment. When dehydration is an associated finding, *fluids* should be given, with enough *sodium chloride* to raise serum levels to normal.

Edema is not usually a problem in acute nephritis, but if it is complicated by acute left ventricular failure it should be treated as vigorously as in non-nephritic patients, except that mercurial diuretics and hypertonic sucrose solutions are to be omitted.

In the presence of hypertension, sharp restriction of salt and fluids, adequate sedation, and oral and parenteral *magnesium sulfate* are in order. A close watch should be kept for signs of cerebral irritation or pulmonary congestion. Preparations should be made in advance for the intravenous administration of *soluble barbiturate* in case of convulsions, for maintenance of respiration, venesection, and oxygen therapy.

Onell and Munoz<sup>34</sup> state that when medical measures fail, surgical treatment may be valuable in the therapy of acute nephritis. Thirty cases were treated by renal decapsulation and denervation, and the authors feel that these procedures are harmless and prevent the progress of the disease. Good results are more frequent when the case has not progressed to the chronic stage.

**Chronic Glomerulonephritis**—Most writers believe that chronic glomerular nephritis is the result of an attack of acute glomerulonephritis, which failed to heal completely. Bell<sup>27</sup> states that "the progress from the latent to the active chronic stage is presumably due to repeated streptococcic infections with progressive obstruction of the capillary circulation." Sometimes the past history of a patient with chronic nephritis will not reveal any history of an acute attack, but this does not exclude the possibility of such an episode, as the acute nephritis may have been so mild as to be over-



looked. At other times, a patient will reveal a history of an acute attack which was supposedly cured. It is generally believed that recurrence of nephritis after complete healing is extremely unlikely. Unfortunately, however, some patients who are actually only in the latent stage, are discharged as cured by the attending physician, only to have their smouldering kidney lesion flare up as a result of increased activity before the proper time.

Chronic glomerulonephritis is four times as common as acute nephritis.<sup>27</sup> The patient is as a rule seen late in the course of the disease when hypertension, anemia, and renal insufficiency have already developed. Albuminuria and edema may or may not be present. The kidneys may be of normal size at autopsy, but they are more often small and contracted. The duration of the disease does not affect kidney size at death. Many of the glomeruli are hyaline and the associated tubules are destroyed. The intertubular connective tissue is somewhat increased due to the contraction of the kidney. Hayman<sup>35</sup> states that there is a reduction in the number of nephrons and that many glomeruli may be destroyed and may disappear completely without much scarring.

According to Hanes,<sup>36</sup> in chronic nephritis the patient exhibits a stare similar to that of exophthalmos. There is retraction of the upper lid, though proptosis is usually not marked. This does not help to distinguish the various kinds of nephritis, but it is useful in differentiating cardiac breakdowns due to chronic kidney disease from those of other types. There is no urinary finding pathognomonic of any one type of Bright's disease, but in chronic glomerulonephritis and acute glomerulonephritis, proteinuria is marked, and hematuria, pyuria, and cylindruria are fairly constant findings.<sup>44</sup>

Chronic glomerulonephritis is attended by a much more serious prognosis than acute nephritis. Cure is usually out of the question, and an early death is probable. Bell noted that in 30 cases in which a definite history of an acute attack was obtained, the duration of life from onset until death varied from one to 25 years, and was on the average ten years.

**Pyelonephritis** — Pyelonephritis has in recent years become recognized as a fairly common disease, and now often is included in the group of Bright's diseases. It is realized that pyelonephritis may cause hypertension and a clinical and pathological picture resembling that of chronic diffuse glomerulonephritis and malignant nephrosclerosis.<sup>26, 37</sup>

In an excellent review of the subject, Prewitt<sup>38</sup> states that the disease occurs most commonly in childhood, pregnancy, and old age. In childhood, the disease is thought to be the result of hematogenous dissemination. The tense abdominal wall pressing on the uterus and the uterus in turn pressing on the pelvic portion of the ureter in pregnancy may produce stasis and eventual renal infection. Hormonal factors may also have an effect in pregnancy. Not much has been mentioned of the cause of this condition in old age.

Pyelonephritis may be caused by infection traveling by the hematogenous route, the ascending or urogenous route, and the lymphogenous route. The hematogenous route is regarded as the most usual in nonobstructive cases. Once the infection reaches the kidney pelvis, it extends into the parenchyma and later into the tubules and glomeruli. Lieberthal feels that in chronic cases, the infection is of low grade, and that the destructive process is aided by the presence of low grade obstruction. The stasis may terminate at any time and the process

may clear up permanently. Sometimes healing is only temporary and recurrent attacks may follow. In other cases the process may smoulder, becoming complicated eventually by hypertension and impaired renal function.

As the disease progresses, the interstitial tissue changes into granulation tissue and the tubular portions become altered. In the acute stage, the kidney capsule strips easily; but in the chronic stage, it does so only with difficulty. The capsule may be thickened. Beneath it the parenchyma appears fine or coarsely granulated, indicating a contracted kidney. Staemmler's four stages of the development of the contracted kidney of pyelonephritis are cited by Prewitt: "The first stage is essentially granulation tissue and inflammatory infiltration with concomitant tubular atrophy; the glomeruli, as pointed out by Lieberthal and Putschar remain quite undisturbed. In the second stage, the glomeruli become involved, there is eventual hyalinization beginning in the parietal leaf of Bowman's capsule, where 'a thin layer of hyalin appears under the epithelium, gradually thickens, and then spreads into the glomerular tuft at the hilus. Finally, the entire glomerulus is converted into a hyalin sphere.' The third stage is mainly confined to changes in the tubular *per se* and due to cortimedullary choking, the tubules have become dilated and filled with a substance that Ponfick has likened to the colloid in a colloid goiter, and indeed in a marked case at first glance, these distended tubules do resemble the acini of the thyroid. The glomeruli are less conspicuous, in marked cases they are hard to find. This accounts for the diagnosis of renal hypoplasia in many cases of actual pyelonephritic contracture. The fourth stage is that of a small, granular kidney in which is seen marked fibrosis, with not

infrequent formation of localized collections of lymphocytes, which collections are called lymph follicles." The process has been called by Longcope and Winkenwerder a slow strangling of the kidney parenchyma in the course of which irregular portions of the kidney are slowly destroyed by inflammation and other portions left unaffected. These investigators believe that since the process is not diffuse, as in glomerular nephritis, nephrosis, or arteriosclerotic kidney, the patient remains free from major symptoms for many years.

Criteria for the histopathological diagnosis of chronic and healed pyelonephritis, according to Weiss and Parker, are: (a) Inflammatory reaction of the interstitial tissue; (b) colloidal casts in the tubules, which are lined with atrophic epithelium; (c) periglomerular fibrosis; (d) evidence of infection or inflammation within the tubules.

The vascular lesions have been studied with particular relation to their bearing on hypertension. Vascular changes are most marked in the scarred areas and are usually confined to the pyelonephritic kidney in the absence of hypertension. The pathogenesis of the vascular lesions is not decided, but Prewitt suggests that they may be degenerative in nature and secondary to the scarring and atrophy of kidney tissue. Hypertension, while a possible complication of pyelonephritis, does not always occur in the presence of this disease. When it is present, the vascular changes are more marked and diffuse.

Treatment with *sulfonamides* may sterilize the urine and terminate the kidney infection, providing the organism responsible for the lesion is susceptible to sulfonamides.<sup>31</sup> A low urinary concentration will effectively sterilize the urine, but higher blood levels are needed for the renal parenchymal infection. High

blood levels should be achieved as soon as possible after diagnosis. If urinary tract obstruction is present, that should, of course, be removed.

**Other Forms of Glomerulonephritis**—In the course of other diseases, a nephritis may be a complicating feature. Lesions resembling those of acute diffuse glomerulonephritis, pyelonephritis, and toxemia of pregnancy have been seen in the kidneys of patients with subacute bacterial endocarditis.<sup>26</sup> Acute diffuse glomerulonephritis is also commonly noted in such diseases as periarteritis nodosa, lupus erythematosus, and Libman-Sacks disease, in which the renal lesions consist of the "concurrence of red cells, red-cell casts, oval fat bodies, fatty casts, broad casts, and heavy proteinuria." Some have considered these reactions as allergic in type.<sup>26</sup> Visceral lesions have been associated with chronic infectious rheumatoid arthritis. Baggenstoss and Rosenberg<sup>39</sup> feel that this is a systemic disease rather than an infection confined to the joints, and showed that changes occurred during its course in the lungs, pleura, liver, and kidneys. Nineteen of 30 patients showed a low grade nonspecific glomerulonephritis. Other renal disorders seen included chronic or subacute interstitial nephritis, nonsuppurative pyelonephritis, amyloid degeneration, nephrolithiasis with acute pyelitis, and dissecting aneurysm of the right renal artery.

Glomerulitis is a finding common to the aged. Gross and Morningstar,<sup>40</sup> after studying 174 patients over 60 years of age, described the glomerulitis as proliferative in nature and involving the tuft, capsule, and capillary endothelium. Sometimes there were adhesions between the tuft and capsule, and hyaline degeneration of the epithelium and endothelium. These changes occurred in about 50 per cent of the 174 individuals studied.

The involvement was mild in 20 per cent, moderate in 13 per cent, and severe in 17 per cent. Nineteen of the patients with severe involvement had hypertension or clinical evidence of uremia. These investigators feel that the proliferative glomerulitis is due to reduction of the amount of functioning renal parenchyma and consequent greater demands on the remaining glomeruli. A similar condition may be caused by hypertension, chronic pyelonephritis, and perhaps other disorders, where the amount of functioning renal parenchyma is not reduced.

### Nephrosis

Lipoid nephrosis is a term used to distinguish the denenerative from the inflammatory type of renal lesion. Like nephritis, it is a glomerular disease, but the basic disturbance is injury to the capillary basement membrane, which allows blood proteins to pass through the capillary wall into the urine. The term is generally applied only to lipoid nephrosis, although some writers include all noninflammatory diseases of the kidney. It has been considered by some to be a tubular disease, and by others a metabolic disturbance with secondary renal damage.<sup>27</sup>

Nephrosis frequently follows upper respiratory infections, but a patient may present no history of infection and edema may be the first symptom. The disease is characterized by an insidious onset, generalized recurrent edema, normal blood pressure, heavy albuminuria, normal blood urea, high serum lipid level, and low total serum protein and albumin. It is a rare clinical entity and was diagnosed by Schwarz, Kohn, and Weiner<sup>41</sup> in only 40 children over a period of 20 years. Of their cases, 22 died. Eight patients were followed for from 7 to 20 years, and of them four developed hypertension, occasional albu-

minuria, and increased Addis counts. Two had increased urinary sediment counts only.

In commenting on the connection of low plasma protein and high plasma lipid in nephrosis, Thomas<sup>42</sup> suggests that deficiency in plasma protein may interfere with the normal transportation and subsequent metabolism of food and depot fat. He is not convinced that nephrosis is a generalized metabolic disease with lipid disturbance as one of its manifestations. The theory that hyperlipemia is secondary to low plasma protein level resulting from albuminuria is, according to him, compatible with the modern view that the high lipid content of the renal tubules in nephrosis is the result of deposition of excess blood fat rather than fatty tubular degeneration.

Emerson and Dole<sup>43</sup> attempted to discover whether the high urea and inulin clearances of nephrosis are due to filtration of an increased fraction of plasma water or to increased renal blood flow by making a series of simultaneous determinations of urea, inulin, and diodrast clearance. They found that both inulin and diodrast clearances were elevated as well as the urea clearances, and concluded that the elevation of urea clearance is due mainly to increased renal blood flow.

Nephrosis may exist either in a pure or mixed form.<sup>27</sup> In the pure type hypertension and renal insufficiency are absent, while in the mixed type one or both of these features are present. Usually patients with pure nephrosis continue to have only pure nephrosis; but, in some cases, hypertension and uremia may develop. When nephrosis is found in children under ten years of age, it usually occurs in the pure form. Bell states that most cases of the pure type and all of the mixed type die. Death follows complicating infections in the

pure type, and in the mixed type it is the sequel of uremia, exhaustion, or inanition. Nephrosis may be seen complicating acute or chronic nephritis. Some patients may experience temporary improvement following acute infections, as measles.<sup>41</sup> The reason for this is not known, but the fact indicates that nephritis and nephrosis are not the same disease.

Pure nephrosis is characterized pathologically by enlarged, yellowish kidneys.<sup>27</sup> Lipoid droplets are found in the proximal convoluted tubules, but signs of serious functional disturbance are not seen. There may be visible thickening of the capillary basement membranes, but often the glomeruli show on changes. In the mixed type there is always a significant thickening of the capillary basement membranes with narrowing of the capillary lumens. When uremia is a feature, the capillaries are much narrowed due to the thickened walls, and the tubules exhibit marked atrophy of disuse. Many of the glomeruli becomes hyaline. The pure and mixed types of nephrosis are not separate diseases, but merely phases of the same process. As the basement membranes thicken, the glomerular capillaries become obstructed, and hypertension and renal insufficiency develop.

The chief problem in the treatment of nephrosis is control of the edema. Preventive measures would do much to simplify treatment. Leiter advises the institution of a salt-free, otherwise adequate diet and the use of milder diuretics as urea or potassium salts in moderate dosage on all patients with proteinuria of more than 2 or 3 Gm. a day and with a plasma albumin of less than 3 Gm. per 100 cc. Treatment is difficult once edema is pronounced, because of the nature of the disturbance of fluid exchange between blood and extracellular fluids.

**Acid-forming salts** and **mercurial diuretics**, when tolerated and when urea clearance is not less than 30 to 40 per cent of normal, are good. **Plasma transfusions** cannot usually be adequate. **Potassium salts** in large doses can be useful, but they have an unfavorable effect on the appetite. Attempts should be made to increase the appetite and combat the physical and psychological effects of complete inactivity. The plasma protein should be built up by increasing the protein intake.

Nephrotic crises are apparently preceded by an accelerated loss of urinary nitrogen and a lowering of the plasma amino acids.<sup>26</sup> Treatment with **intravenous amino acids** or **casein hydrollysates** may help prevent fatalities from nephrotic crises, though it will not prevent or relieve them.

### Nephrosclerosis

Nephrosclerosis may occur in the benign or malignant forms. Mansfield, Mallory, and Ellis<sup>44</sup> state that malignant nephrosclerosis tends to be a disease of early middle age and youth, whereas the benign form occurs after 50 years of age. The malignant type of nephrosclerosis runs a short course of two years or less, but the benign form carries a better prognosis. Both types of nephrosclerosis are characterized by a terminal prominent arterial hypertension. Of ten cases of malignant nephrosclerosis, these authors found that nine had retinitis with papilledema. Uremia of long duration is common in benign nephrosclerosis. There may be an anemia which is generally proportional to the degree and duration of renal failure. Heart trouble may be a common primary or contributory cause of death. Cerebrovascular symptoms are frequent in cases of malignant nephrosclerosis.

Nephrosclerosis has been produced experimentally in chicks by overdosage with desoxycorticosterone acetate, and this may be taken to mean that adrenal-cortical involvement is a factor in the production of nephrosclerosis. Selye and Stone<sup>45</sup> studied the influence of salt in the production of nephrosclerosis by steroids. They found that concentrated salt solutions will cause generalized tissue edema and nephrosclerosis in chicks. Desoxycorticosterone acetate produces the same results even when salt intake is normal and sensitizes chicks to threshold doses of sodium chloride. Progesterone also has the same effect, although it is not as active as desoxycorticosterone acetate. This may indicate that disturbances in water metabolism and certain kinds of nephrosclerosis may develop in man following excessive production of desoxycorticosterone acetate, progesterone and related steroids. Kidney changes are described by the authors as consisting of hypertrophy and sometimes cloudy swelling of the tubules with desquamation. Many tubules contained hyaline casts. The glomeruli were enlarged and often the cells of the parietal lamina of Bowman's capsule were unusually high. Hyalinization of the glomerular capillaries and proliferation of the epitheloid cells in the region of the glomerular capsule occurred to some extent. Raab<sup>46</sup> noted that in nephrosclerosis there is a high sugar threshold, and that epinephrine may raise the renal threshold for sugar excretion.

### Edema

Renal edema depends upon pathologic physiological changes in the fluids and tissues of the body rather than upon pathological changes in the kidneys, as was believed at one time. Edema of renal origin can be divided into the acute and chronic. Chronic nephritic edema

seems due chiefly to plasma protein deficiency and the acute sort to increased capillary permeability. Sodium chloride consumption may cause or augment edema when there is hypoproteinemia. Edema does not occur in all types of Bright's disease and is often absent in those cases with the most marked kidney insufficiency. In the presence of edema there is albuminuria, decreased concentration of plasma protein, and increased sodium chloride in the plasma and tissues. The colloidal osmotic pressure of plasma is lowered. There is hypercholesterolemia and a low basal metabolic rate. Plasma volume is diminished.

Abramson, Fierst, and Flachs<sup>47</sup> found that in edema the peripheral circulation is increased and not decreased, except when congestive failure is present, when it is normal. This increased blood flow does not seem to be due to increased venous pressure alone, as in edema the venous pressure may be normal even when blood flow is increased. It is agreed that edema fluid interferes with the free interchange of oxygen between blood and tissues and the removal of wastes and the other end products of metabolism. Anoxia from this and/or an accumulation of vasodilator substances locally might produce arteriolar vasodilatation and an increase of blood flow to the edematous part. Smith, Goldring, Chasis, Ranges, and Bradley<sup>15</sup> report that administration of saline may reduce the tubular maximum reabsorption of glucose and thus play a part in renal edema and increased intrarenal pressure. There is generally a simultaneous increase in total filtration rate and effective renal blood flow, which may mean that renal edema is accompanied by hyperemia as occurs in other tissues.

The work done by Keith, Binger, and Osterberg<sup>48</sup> indicates that *redissolved dried human blood plasma* can be

given intravenously with safety to patients with edema and hypoproteinemia. It may or may not produce diuresis, however, depending on whether or not the serum protein increases and the urinary protein loss is not too great. If too much protein is lost in the urine, enormous doses of plasma may be needed and its administration may bring up a serious economic problem. The fact that redissolved dried blood plasma is beneficial to some patients with nephrotic edema suggests to these authors that other solutions, as *acacia*, *dried serum* or *plasma*, and possibly *isinglass* and *pectin*, may do good where other procedures have failed. Some have noted, however, that acacia may produce liver damage with impaired hepatic regeneration of protein.<sup>188</sup>

Lehnhoff and Binger<sup>49</sup> state that in nephrosis and chronic nephritis when edema is present, it is often the predominant symptom, and hypertension with its associated blood vessel changes of the brain, heart, and kidneys is absent. Renal function is good, and there is no nitrogen retention or anemia. They believe that this kind of edema may be cured by treatment aimed at removing the excess sodium chloride from the body by way of the urinary tract. Serum protein must be augmented and the intake of water and salt restricted. Treatment is based on dietetic and diuretic measures which restore the physicoelectrolytic balance in the body. The authors reported good results in a group of 12 patients managed in this manner. According to their regime, diet consists of 100 to 125 Gm. protein daily and no salt except for that naturally found in food, and between 1000 and 1500 cc. of fluid daily. If the edema-free weight is normal, the diet should contain about 2000 calories. It may be supplemented with *vitamins* if necessary, and it is essential

that it be adequate. *Gum acacia* was used as a diuretic. Each patient received a minimum of three intravenous injections of 500 cc. of 6 per cent solution of pure acacia in a 0.06 per cent solution of sodium chloride at intervals of one to two days. Sometimes more was necessary. Treatment was stopped if the concentration of acacia was 2 Gm. or more per 100 cc. serum. Otherwise, it was continued until the patient was edema-free and the blood acacia level was satisfactory. Some patients had mild headache, backache, and a sensation of constriction in the thorax, but these symptoms were relieved by slowing the rate of flow of acacia into the vein or giving a little *epinephrine* or *ephedrine*. Focal infections were removed. On dismissal, dietary instructions were given to the patient and he was advised to take *potassium nitrate* until advised otherwise by a physician. A course of acacia may be given prophylactically in some cases. In other cases, a subsequent course may be necessary to control recurrent edema.

### Hypertension

Hypertension is not a disease entity but a manifestation of a diffuse vascular disease. Its significance depends on the associated pathology of the brain, eye grounds, heart, and kidneys. In order to bring about more successful management of this entity, an etiologic, pathologic, and physiologic diagnosis should be established in every patient with hypertension.<sup>50</sup> This is often difficult to do, and many theories have been passed on the question of the etiology of hypertension, especially in regard to its relation to the kidney.

There are two main types of hypertension: (1) The renal kind in which the kidney holds the center of the stage; and (2) essential hypertension, in which

the heart is the organ chiefly at fault.<sup>51</sup> The patient with renal hypertension presents a history of kidney difficulty in adolescence. Hypertension is not necessarily very high, but there is associated edema, and evidence of renal insufficiency which indicate the diagnosis. The course of the disease is short, from five to ten years, and is marked by relapses and remissions. Death is usually due to renal failure and uremia. Glomerulonephritis or another of the nephritides is most frequently responsible for this type of hypertension, but other conditions as stones, cysts, tumors, diseases of the kidney as tuberculosis, and anomalies of the urinary tract are also occasionally involved.

Essential hypertension, which comprises most of the cases of hypertension, is divided into the benign and malignant type. Ninety per cent of essential hypertension is benign and only 10 per cent malignant. Benign hypertension is characterized by high blood pressure, cardiac enlargement, and an asymptomatic course. Death is usually caused by heart failure, or sometimes apoplexy or uremia. The kidney appears innocent, and renal function tests are normal except for a trace of albumin. The disease occurs as a rule in patients over 40. Such a patient may have high blood pressure for 10 to 15 years before headaches, shortness of wind, chest pain, or general malaise cause him to seek medical advice.

Malignant hypertension is not really a separate and distinct disease as much as a more severe phase of essential hypertension. It comes on commonly in patients younger than 40 years of age, and is characterized by a more severe and rapid course than that of benign hypertension. Headaches may be almost unbearable, and there is a rapid loss of weight and appetite. Diastolic pressure mounts to 130 to 150 mm. Hg. Vomit-



ing is of frequent occurrence. An outstanding sign of malignant hypertension is bilateral choking of the disks, fresh and old white patches scattered throughout the retina, and new and old hemorrhages of varying size. The retinal edema may be so great that the constricted bloodless arterioles may be entirely obscured. After a stormy course of one or two years, the patient dies abruptly of uremia.

Both benign and malignant hypertension are associated with arteriosclerosis of the renal arteries and arterioles, but in the malignant form the arteriosclerotic process is more widespread and is further distinguished by the presence of necrotic lesions throughout the arterioles of the kidney. Scheinker<sup>52</sup> noted that all hypertensive patients showed typical vascular alterations of the brain confined to the arterioles and capillaries. These changes consisted of hyaline degeneration and fibrotic thickening of the walls associated with narrowing or obliteration of the lumens. These arteriolar changes are a type of arteriolopathy peculiar to hypertension and different from that usually found in arteriosclerosis. Prolonged or repeated functional vascular disturbance is probably responsible. Parenchymal changes in the brain consist of diffusely scattered, circumscribed small foci of old and recent softening, perivascular hemorrhage, massive hemorrhage, and diffuse or localized edema. The changes seen in the brain tissue are probably secondary to the arteriolar lesions.

The renal theory of hypertension may be given briefly thus: Compression of the renal artery by the Goldblatt clamp, or of the entire kidney by the Page perinephritic capsule will be followed by hypertension according to animal experimentation, if the renal circulation of blood is sufficiently impaired. Reduc-

tion of pulse pressure is more important in the elevation of blood pressure than the production of ischemia to the kidney. Apparently blood passing through such kidneys becomes pressor in effect, and when circulated through the body causes generalized vasoconstriction and hypertension. An abnormality found in all hypertensives occurs in both kidneys and consists of a glomerular filtration rate high in proportion to the total renal blood flow and tubular excretion, which are decreased to some extent. This may be an indication that there is vasoconstriction of the efferent arterioles of the glomeruli, and it may represent the vasoconstrictor response within the kidneys to the humoral pressor material liberated by the abnormal kidney. The pressor material concerned is known as renin, or hypertensin. Renin alone cannot cause hypertension, but when allowed to interact with a substance in the blood called "renin activator" another substance called "angiotonin" is formed, and this angiotonin can and does raise blood pressure. It has also been postulated that the normal kidney contains an inhibitor substance, which will counteract the effects of angiotonin and either prevent or cure hypertension.<sup>53, 54</sup>

The rise in the blood pressure in experimental, essential, and angiotonin hypertension is peculiar in that the heart beat is augmented, resulting in overactivity and enlargement, and constriction of the peripheral arterioles without reduction of blood flow. The principle change in the kidney is constriction of the small arterioles proximal and distal to the glomeruli which results in increased pressure within the glomeruli and reduction of the peritubular blood flow. The result is artificially elevated urea clearance and reduced ability to concentrate urine. Insulin and diodrast tests are valuable in the study of the

intrarenal dynamics occurring in hypertension.<sup>55</sup>

In applying this theory clinically, the counterpart of the Goldblatt clamp or Page's perinephritic capsule in the etiology of hypertension has been considered to be such conditions as unilateral kidney diseases,<sup>56, 57, 58</sup> abdominal or gynecologic tumors displacing parts of the urinary tract,<sup>59, 60</sup> and other anomalies of the ureters and kidneys. There is, however, much disagreement on what can and what cannot cause renal hypertension.<sup>61, 62, 63, 64</sup> Shrader, Young, and Page<sup>65</sup> made a study to determine whether or not there is a characteristic pyelogram in hypertensives, and if abnormal urograms are more frequent in unselected hypertensives than in unselected normotensives. They found that there was little or no difference in the retrograde pyelograms of hypertensives and nonhypertensives, and that abnormalities are no more common in hypertensives than in others. Hayes and Ashley<sup>66</sup> found that the past history of 55 cases of advanced hypertension revealed a high incidence of bedwetting and chills and fevers during childhood. Twenty-six of 33 women had had toxemic pregnancy or pelvic operation or both. Fifty-four and five-tenths per cent of the group had obstructive lesions of the lower urinary tract, and 60 per cent showed various changes in the upper urinary tract commonly attributed to urinary back pressure. Other lesions included renal calculi, ureteral calculi, renal cyst, polycystic disease, duplication of ureters and pelves, and ptosis of one or both kidneys. They feel that the lesions found were sufficient in number and importance to suggest a urological examination of all cases of hypertension, not only to improve the urinary tract findings but to find and correct the cause of the hypertension. Arteriosclerosis of the

renal artery has been thought to cause renal ischemia sufficient to induce hypertension. However, Castleman and Smithwick,<sup>63</sup> after doing renal biopsies on 100 hypertensives, found "that the morphologic evidence of renal vascular disease in more than half of the cases was inadequate to be the sole factor in producing hypertension and that in many of these and probably others, the hypertensive state antedated the renal vascular lesions which, once established, probably aggravated the hypertension." Lisa, Eckstein, and Solomon,<sup>67</sup> after a study of the condition of the main renal arteries in 100 cases coming to autopsy, could find no consistent relation between the state of the renal arteries and hypertension. The condition of the kidney arterioles seemed to bear more relation to the hypertension than the state of the main renal arteries. These authors feel that this supports Page's theory that hypertension is due to lowering of the pulse pressure in the kidney. Pickering<sup>68</sup> states that in essential hypertension, the elevated blood pressure may be accounted for by arteriolar constriction. This constriction does not seem to affect the vessels to voluntary muscles much if at all. It affects the skin and cerebral vessels just enough to counter the effects of raised arterial pressure on the blood flow. The efferent glomerular arterioles are constricted in the kidney and blood flow there is reduced. The agent is not nervous but chemical. The circulation in nephritic hypertension is probably not different from that of essential hypertension and is also probably humoral in origin. However, since the vessels of neither the hand nor kidney are constricted, the cause of hypertension seems to be different. The agent may be nervous, but nothing has been proved in regard to it.

Experimentation done to ascertain the part of ischemia in producing hyperten-

sion caused Corrigan and Pines<sup>69</sup> to conclude that hypertension depends on a disturbance of the balance between arterial and venous pressure in the kidney. When the balance is disturbed in favor of venous pressure, stasis takes place in the renal capillaries and primary renal circulation is short circuited through arteriovenous shunts. Kidney tissue accordingly gets too little blood and starts putting out a hypertensive substance. When the balance is restored between venous and arterial sides of the kidney, the hypertensive substance is no longer produced, as there is again enough oxygenation. Raska<sup>70</sup> found that the ischemic kidney *in vivo* shows a diminished rate of tissue respiration and a disturbed enzymic equilibrium, and suggested that those disorders responsible for the formation of the renal pressor hormones in dogs made hypertensive by the Goldblatt, Page, or Taylor method. Davis and Poser<sup>71</sup> comment that since renin is not as a rule found in those with chronic primary or secondary anemia or in conditions in which the oxygen content of the blood is low, the formation of renin is not due to a lack of oxygen in the kidney. It seems due rather to relative or absolute deficiency of the elements needed for the production of respiratory enzymes needed in normal dehydrogenation and deamination of amino acids by oxidation in kidney cells and normal suprarenal metabolism.

Friedman and Kaplan<sup>72</sup> have done extensive work on the site of renin formation in mammals. It had formerly been noted by them that though the kidney of fresh water fish contained renin, the kidney of marine fish did not, whether glomeruli were present or not. In another study it was found that the mesonephros and metanephros of the hog fetus contained renin, though neither of these kidneys possessed Goormaghtigh

cells and that the renin content depended on the activity and structural integrity of the convoluted tubular mass rather than on the arterioglomerular component. Recently by giving tartrate to adult rabbits, they produced in some of them widespread and severe necrosis of the proximal convoluted tubular epithelium without affecting the other portions of the nephrons. The damaged kidneys were found to be almost devoid of pressor substance (renin), showing that in the mammalian kidney the epithelium of the proximal convoluted tubules is concerned in the formation or storage of renin.

The juxtaglomerular apparatus has been considered a site of the origin of hypertension. Under the fluorescent microscope, bright, fluorescent granules are seen in the juxtaglomerular apparatus of some human kidneys.<sup>73</sup> The granules may be dissolved by lipid solvents and are distinct from other fluorescent particles in the kidney. They are absent in children, and increase in incidence, size, and number with age. In essential hypertension they are marked, but in nephrosclerosis and nephritis they are reduced. The type of fluorescence, the lipoid solubility, appearance in smooth muscle cells all suggest that these granules are wear and tear pigment and that they may represent a common pathologic process, as arteriosclerosis. The cells with the most marked fluorescence were characterized by vacuolization, and bizarre changes of the nuclei, and hyalinization or connective tissue proliferation between the cells. The fluorescence and pathologic changes, which are also found in hypertension, refute the assumption that the cells form renin. It is suggested by Popper and Loeffler instead that the juxtaglomerular apparatus may be concerned in the neutralization of renin.

The importance of the renal theory of hypertension is by no means accepted by

all.<sup>74, 75</sup> Leiter and Eichelberger<sup>76</sup> note that renin hastens the pathological process of experimental malignant hypertension in dogs with excessive renal ischemia or necrosis and also in some dogs without severe hypertension or uremia. Prolonged effects followed the administration of renin in conscious dogs with marked renal changes. The authors feel that this favors the renin etiology of experimental renal hypertension and the view that the ratio of normal to abnormal renal parenchyma determines the dog's response to exogenous and endogenous renin. They state, however, that the place of renin in the etiology of human essential hypertension is not yet settled.

According to Warthin and Thomas,<sup>77</sup> chronic renal hypertension can exist in the presence of normal renal blood flow. They made five dogs hypertensive by partial occlusion of the renal arteries and found that just before or at the same time as hypertension started, there was a reduction of renal blood flow and phenol red excretion. Renal blood flow returned to normal in three or four weeks and phenol red excretion in four to seven weeks, but hypertension persisted. Pentobarbital anesthesia was followed by a reduction in blood pressure and renal blood flow before and after hypertension occurred.

Smith, Goldring and Chasis<sup>78</sup> feel that the kidney is the "victim rather than the culprit" in the genesis of essential hypertension. The kidney may play an intermediary rôle, though this, like the whole etiology of essential hypertension, is unknown. Renal ischemia is not the cause and is secondary to the presence of vasoconstrictor substances in the blood. They feel that primary arteriolar disease, etiology unknown, is a more probable causative agent. The Goldblatt technic does produce hypertension, but these au-

thors are not convinced that essential hypertension develops this way clinically.

Besides the renin theory, other substances have been suspected of inciting hypertension. Van Euler and Sjostrand<sup>79</sup> found a pressor principle in the urine of normal persons, isoamylamine, which accounted for most of the urine pressor action. Extracts of this substance from normal kidneys have a strong pressor action. This substance is not so abundant in the urine of patients with chronic nephritis and hypertension. This finding suggests to the authors that important changes in the production or excretion of biologically active metabolites occurs in essential hypertension. Alonso, Croxatto, and Croxatto have noted that pepsitensin acts in a manner similar to hypertensin.<sup>134</sup> Pepsitensin is a vasoconstrictor and hypertensive substance, which is formed by digesting the blood plasma globulin, hypertensinogen, with pepsin at pH 2-6. Tyrosine has a hypertensive effect, possibly due to the excessive tyramine formation from tyrosine. It was found by Martin<sup>80</sup> that extracts of blood from hypertensive patients, those with nephritis and nephrosclerosis, are vasoconstrictive when injected into animals and were found to contain tyramine. Diets containing an amino acid composition (five and ten per cent tyrosine) which would yield on decarboxylation predominantly pressor amines were given to rats. The rats developed hypertension. In a later publication Martin and Hueper<sup>81</sup> reported that diets high in tyrosine cause hypertension and pathological changes including perivascular fibrosis, arteriolar medial degeneration in various tissues, and regressive and necrotizing changes in the parenchyma of the pancreas and kidney. The basic biochemical lesion is thought by them to be a decarboxylation of tyrosine to produce tyramine. This occurs in the kidney

where tyrosine decarboxylase is most concentrated. The local tyramine production in the kidney causes a renal ischemia and sets into action the mechanism responsible for experimental renal hypertension.

Chronic slight dietary deficiency, especially of vitamin B,<sup>71</sup> has been blamed. The importance of hereditary influences on the development of hypertension has been considered important. Lawrence,<sup>82</sup> in a study of 220 college students, found that 9.5 per cent of them had abnormal pressures and that most of them came from hypertensive families. On the other hand, Feldt and Wenstrand<sup>83</sup> state that heredity is probably not of primary importance in the genesis of hypertension. The endocrine aspects of hypertension are reviewed by Goldzieher and Salmo-vitz,<sup>84</sup> who state that there seems to be a relationship between changes in blood pressure and abnormal conditions of the endocrine glands. It was discovered that salt and water loss resulted in hypotension, and salt and water retention in hypertension. A relation was felt to exist between blood pressure and salt and water retention in hypertensives with endocrine disorders. The posterior pituitary was thought by some to play a rôle in the genesis of experimental renal hypertension, but studies<sup>85</sup> showed that the excretion of the urinary antidiuretic principle in dogs during normal hydration and dehydration was not affected by the production of experimental hypertension. It had formerly been suggested that diethylstilbestrol can cause hypertension, but this theory was disproved by Matthews, Emery, and Weygandt,<sup>86</sup> who gave 45 adult oöphorectomized rats and 35 normal male rats 1 mg. diethylstilbestrol in alkaline aqueous medium by stomach tube daily for periods up to 100 days without noting any effect on blood pressure, heart, or respiratory

rates. The administration of an overdosage of desoxycorticosterone acetate, especially in the presence of a high salt diet, in rats caused a marked elevation in blood pressure, marked diuresis with increased excretion of sodium and chloride, proteinuria, and clinical signs of severe cardiac decompensation. Hemorrhagic and lung edema brought about death in some cases. The pathological findings resembled closely those of hypertensive heart disease of renal origin and are described by Selye, Hall, and Rowley<sup>87</sup> as "hypertrophy and capsular fibrosis of the renal glomeruli with hyalinization of their tuft capillaries. Fibrosis, hyalinization, and even actual necrosis of the arteriolar walls is evident not only in the kidney itself where the vasa afferentia are particularly affected, but also in the pancreas and the adrenal capsule. In the pancreas these vascular changes are frequently accompanied by edema and pronounced stroma proliferation."

In considering the adrenal cortex in the etiology of hypertension, it is interesting to note that Sarason,<sup>88</sup> discovered changes in the adrenal glands in hypertensive patients. Twenty patients with hypertension were studied. All had cardiac hypertrophy and 13 also had nephrosclerosis. The average combined weight of the adrenals was 15.9 Gm. The most striking feature was the abundant lipid in the widened cortex. There was adenomatous hyperplasia of the adrenals in 5 cases. The increase of lipid applied to the inner as well as to the outer zone. Only 3 cases with inflammatory disease had foci of lipid depletion in the outer part of the zona fasciculata. In the other 7 hypertensives, who had chronic glomerulonephritis or pyelonephritis, the average combined weight of the adrenals was 12.58. Excessive lipid was in the cortex in 4 cases. Two had lipid

depletion in the zona fasciculata. The seventh case had normal lipid distribution. These changes are most prominent in the presence of primary vascular disease.

Price<sup>89</sup> presents data to show that there is a connection between food allergy and hypertension. According to his findings, hypertension may be aggravated by food allergy, or it may result from an accumulation of minor allergens. Total protein content is not as important as the specificity of the protein, and other factors may also be concerned. Animal proteins are not the most common offending agents. Except where the hypertension is far advanced and nephrosclerosis of severe degree is present, hypertension may be helped by searching out the offending allergen, and making up a diet for the patient. Variety in the diet without repetition of possible allergens is emphasized.

Renal hypertension, rheumatic lesions, and periarteritis nodosa may all be due partially at least to abnormal, probably excessive, adaptive responses of the adrenal cortex, and represent diseases of adaptation.<sup>90</sup> Selye and Pentz noted that the toxic effects of chronic desoxycorticosterone acetate overdosage are enhanced by nephrectomy, and that severe overdosage with this drug was followed in the rat by lesions resembling those of periarteritis nodosa, malignant hypertension, and rheumatic fever. In humans these diseases are often preceded by infections, exposure to cold and in animals similar changes appear in the course of adaptation to cold and other noxious stimuli. It is thought that during adaptation the adrenal cortex increases in size and produces too much corticoids.

May<sup>91</sup> feels that the problem still depends chiefly on a central nervous system disorder, rather than on endo-

crine or metabolic factors, and believes hypertension may be associated with constitutional or hereditary vascular weakness. Gregory, Lindley, and Levine<sup>92</sup> favor a vasomotor etiology of central nervous system origin to the humoral theory of essential hypertension. They based this assumption on experiments with spinal anesthesia on normal and hypertensive patients. They found that in normal patients, spinal anesthesia had little and often no effect on blood pressure, but that it caused a marked lowering of blood pressure in hypertension, even when the hypertension was of renal origin. According to them, this would indicate that the fall of blood pressure was not due to improved renal circulation, and that it was due to vasomotor impulses. The long action of the humoral substances causing renal hypertension, and the rapid fall seen in essential hypertension treated with spinal anesthesia makes it seem likely that essential hypertension and that due to renal ischemia are caused by different substances.

Increase of intracranial tension can cause hypertension.<sup>93</sup> Ligation of the arteries supplying the head in dogs is followed by hypertension, possibly due to hypertensive substances being formed by the ischemic brain. Removal or manipulation *in situ* of the carotid sinuses alone does not have a prolonged effect on dog's blood pressure.<sup>94</sup> Forster<sup>95</sup> states that general hypertension resulting from increased intracranial pressure will not occur unless the medulla is intact. The neural structures rostral to the medulla are unnecessary for this hypertension. If the medulla and pons are anatomically separated from the higher structures, the response is enhanced.

The question of what is and what is not normal in blood pressure has been much discussed. Russek,<sup>96</sup> after a study

of 1000 male subjects between the ages of 60 and 95, found that the average systolic pressure and pulse pressure increase significantly with age, but that the diastolic pressure does not vary much after 65. Very few people over 65 have a so-called normal blood pressure. Those with a systolic hypertension had a normal life expectancy, while those with elevated diastolic pressures did not live so long. Russek suggests that systolic hypertension in the aged is normal, and that more study of atherosclerosis may show that it is physiologic. Masters,<sup>97, 98</sup> in a study of naval recruits, also found that high blood pressures after the age of 40 are so frequent, that they may not be abnormal in all cases. However,<sup>99</sup> he feels that one high reading is all too frequently a sign of impending serious hypertension. He suggests that before naval recruits who have had one or more high readings are accepted into service, they should be subjected to intensive examinations for organic heart disease, vascular and kidney disease. Eyeground examinations should be done also. Before final admittance, such recruits should sign a waiver absolving the government of liability in case of a future onset of hypertension with its attendant complications.

The cold pressor test has been regarded as a valuable means of detecting hypertension and the prehypertensive stage. Russek,<sup>100</sup> however, in observations made on 200 normal subjects over the age of 40, found that there was so high an incidence of hyperresponse in normal subjects over the age of 50 that the test was unreliable in the diagnosis of latent hypertension in subjects over 40, and that hyperresponsiveness to cold in persons over 40 years of age is unrelated to essential hypertension. The response of hypertensive persons to stimuli was studied by Cohn, Burch, Neu-

mann, Rule, Sellers, and Lhamon.<sup>101</sup> The experiments were done on subjects who were as nearly relaxed as possible. Results showed that hypertensives react in much the same manner as others to stimuli except that the reaction is quicker and the duration after cessation of stimuli is longer.

**Treatment**—The treatment of essential hypertension may be classed into the surgical, medical, and kidney extract therapy. The medical treatment is largely empirical and consists of treatment with various vasodilators and hypotensive drugs. The psychosomatic factors are most important in treatment; but drugs, sedatives, and hypnotics are also unfortunately needed. The response to drug therapy is at the best unpredictable, and no drug is completely satisfactory in the control of hypertension. *Potassium thiocyanate* has been one of the most popular of these drugs and in some individuals produces satisfactory results.<sup>112</sup> However, it should be carefully controlled by frequent appraisals of blood concentration. If this cannot be done, the drug should not be given.<sup>102</sup> Severe reactions may develop from potassium thiocyanate therapy, and a toxic psychosis followed by death in uremia was reported by Solomon, Greenblatt, and Coon.<sup>103</sup> *Sodium sulfocyanate*<sup>104</sup> may be valuable in treatment of cases not complicated by cerebral accidents, severe kidney or coronary disease. It should not be used on weakened individuals or on those in the older age groups. Studies by Petersen on 33 patients with essential hypertension showed that symptomatic relief was satisfactory in about half the cases and only fair in another 35 per cent. Systolic blood pressure dropped from 30 to 50 mm. Hg. in 16 of the 33 patients and 21 had a drop of from 10 to 30 mm. Hg. in diastolic pressure. The dosage varied with renal



function, but usually was 0.165 Gm. (2:5 gr.) twice a day at the beginning. Fanson, Kinsey, and Palmer<sup>105</sup> used potassium sulfocyanate on 100 patients with essential hypertension over a period of 5 years. Blood pressure was relieved in 28 per cent of the patients, but its most valuable effect was symptomatic relief, particularly of the headache. The drug was used cautiously, and only one-fifth of the patients had toxic reactions. However, the authors stress the fact that the drug is potentially dangerous and that there is only a narrow and variable margin between toxic and therapeutic levels. They suggest that the standard optimum therapeutic levels are not necessary for a hypotensive effect. Those who received insufficient relief from the sulfocyanate often had levels of 8 to 12 mg. per 100 cc. or more, while the hypotensive action occurred at levels below 8 mg. per cent in over half the patients.

On the hypothesis that loss of salt and water would lower blood pressure associated with endocrine disorders, Goldzieher and Salmovitz treated 100 hypertensive patients by placing them on a *diet low in carbohydrate, salt and liquid and high in protein*.<sup>84</sup> Underweight individuals received supplementary fat to prevent weight loss. ***Ammonium chloride***, 0.486 Gm. (7.5 gr.) in enteric coated tablets, t.i.d., was given to increase the urinary excretion of sodium chloride. After 5 days, this treatment was switched to ***potassium acetate*** or other organic potassium salts to further increase chloride excretion. Sedation with ***atropine sulfate*** and ***phenobarbital***, and ***endocrine therapy*** are recommended as needed with this therapy. Treatment in these cases resulted in a considerable drop in blood pressure which was maintained over a prolonged period of time.

***Vitamin A therapy*** in the management of hypertension is beneficial, according to Villaverde,<sup>107</sup> who reported success in 25 of 100 cases and satisfactory results in 50 patients. However, Wakerlin and Moss,<sup>108</sup> in a follow-up of their more optimistic report of 1942, felt that the good results they had observed with vitamin A dissolved in sesame oil were due to some other substance than vitamin A. They tried the vitamin A concentrate in sesame oil in a dosage of 200,000 units daily for three months on dogs and followed this by another course of 400,000 units daily for three months. Hypertension was reduced considerably. However, other lots dissolved in sesame oil, fish liver oil, and purified vitamin A alcohol in sesame oil, and another lot dissolved in fish liver oil and subjected to heat inactivation of the vitamin A and sesame oil did no good. Blumenthal and Wetherby<sup>109</sup> gave vitamin A to 20 unselected hypertensives in doses up to 200,000 international units daily for two weeks, followed by 100,000 international units daily for 6 to 12 weeks with equally negative results. Grollman and Harrison<sup>110</sup> found that fish body and liver oils contained a material effective in lowering blood pressure of hypertensive rats. The oils were made more effective by oxidative processes which destroy vitamin A, indicating that vitamin A is not an antipressor substance.

Other recommended forms of medication are the administration of ***vitamin C***,<sup>71</sup> 1 Gm. (16 gr.) ***ascorbic acid*** daily, and ***adrenochromes***. Adrenochromes, 5 to 100 mg. in 0.5 to 1.0 cc. of olive oil as a vehicle, were given to rats intraperitoneally or intramuscularly by Oster and Sobotka.<sup>111</sup> Reduction of hypertension occurred, but normal blood pressures were not affected. Toxic manifestations or fever were absent.

Until some more reliable method than those so far discovered has become available, the most important consideration in the management of the hypertensive patient is regulation of his life. This entails the golden mean of moderation in all things. The diet does not have to be rigidly controlled, but too much food should not be taken. Liver, kidney, or meat extracts should be excluded and tea, coffee, and tobacco should be used only moderately. *Bed rest on a low diet* is helpful in acute cases. Sleep must be adequate and exercise mild and gentle. Rest after meals is important. Business activity should be given up if possible, and the patient should be taught not to worry about his blood pressure. Life should be made pleasant for the patient in all ways, that is, mentally, emotionally, and physically.<sup>106</sup>

Treatment with renal extract presupposes that hypertension is caused by a renal pressor substance liberated from the ischemic kidney, and that this substance is inhibited by a renal extract.<sup>113</sup> Results of treatment have not been brilliant, but occasionally good effects are noted. Murphy<sup>51</sup> used *kidney extract* on 16 patients over 2 years and, of these, 6 improved (2 with malignant hypertension and 3 with benign), 4 showed no improvement (1 malignant and 3 benign), and 6 died (5 malignant, 1 benign). Wakerlin and his colleagues<sup>114</sup> prevented experimental hypertension of renal origin in 6 of 15 dogs by daily intramuscular injections of certain partly purified renin solutions for 3 months before and 3 months after constriction of the renal arteries. Two of the four dogs were protected by hog renin, one by rabbit renin, and none by inactive human renin. Renal hypertensive dogs responded to partially purified hog renin injected intramuscularly for four months or more. Three of four dogs success-

fully treated a year before responded just as well to hog renin on the second course. Two dogs who were previously unaffected by inactivated hog renin and dog renin responded to the second course of hog renin. The mechanism of these reactions is not known. It may be due to renin or some other substance in the partially purified renal extracts, but antirenin is probably not concerned according to these investigators.

The specificity of treatment with renin has been challenged by many. However, Rodbard and Katz<sup>115</sup> implanted 10 to 30 Gm. of fresh dog kidney subcutaneously in dogs, a procedure which resulted in abscess formation in 48 to 72 hours and in reduction of blood pressure of dogs with renal or essential hypertension. Similar treatment of normal dogs did not have any significant effect on blood pressure. Abscesses were also made with implantations of fresh muscle, liver, and spleen, but these had no appreciable effect on the hypertension. This would indicate that nonspecific reactions do not account solely for the depressor effect of kidney implants. Page and his colleagues<sup>116</sup> also feel that pyrogenic and local tissue reactions alone do not reduce blood pressure. The effect of the extract, according to them, depends on the ability of the extract to neutralize angiotonin. Weinstein, Friedman, Newman, and Sugarman<sup>117</sup> found that blood from a kidney in which the arterial flow and pressure is much reduced is less vasoconstrictive than normal kidney blood and it also has less ability to neutralize angiotonin. Considerable work has been done in the past year on study of the properties of renin, renin activator and hypertensin, and in obtaining a purified renal extract.<sup>118, 119, 120, 121, 122, 123, 124</sup> It is to be hoped that out of these investigations will come a clearer understanding of the part renal extract plays in

lowering blood pressure. Grollman and Harrison<sup>110</sup> find that *fish body* and *liver oils* and *kidney extracts* are very similar in physical and chemical properties and almost identical in their effect on blood pressure. Since fish oils are a more practical source of antipressor material than kidney extract they may offer a greater promise as a source of a therapeutic agent for hypertension than kidney extracts.

In certain selected cases, *surgery* is followed by cure of the hypertension.<sup>125</sup> The surgical treatment of hypertension varies from surgical removal of a diseased kidney to several different types of operations on the autonomic nervous system, all of them distinctly in the class of major operations. If the hypertension is actually being caused by the diseased kidney, nephrectomy will do good. However, a kidney may be diseased without causing hypertension. Weiss and Chasis<sup>126</sup> report a case of chronic atrophic pyelonephritis associated with hypertension. The kidney was removed, but the hypertension did not improve. This could not be blamed on the remaining kidney, since it was neither diseased nor ischemic. *Sympathectomy* has been used by many, and, according to Fulcher,<sup>127</sup> in carefully selected patients, 50 per cent will have excellent results, and 80 per cent good results. About 20 per cent will not experience any change in blood pressure, though symptoms may be decreased and blood chemistry may become normal. Other observers<sup>128</sup> do not feel that surgical operations have any specific effect on blood pressure, and believe rather that the reduction of blood pressure and improvement of subjective symptoms are due to nonspecific effects of operation. *Bilateral radical lumbo-dorsal splanchnicectomy* has very little effect on renal clearance, glomerular filtration, and renal plasma flow, according

to Talbott, Castleman, Smithwick, Melville, and Pecora.<sup>129</sup>

Sympathectomy is usually most beneficial in patients with the highest effective renal blood flow, the greatest vasomotility and least thickening of systemic arterioles. Therefore, tests of effective renal blood flow, the wall/lumen ratio of systemic arterioles in biopsy specimens of muscle, the intensity of the vasomotor reactions and eyeground examinations should be done before subjecting a hypertensive patient to surgery.<sup>130, 133</sup> *Paravertebral alcoholic block* done preoperatively offers a good way of prophesying the result of sympathectomy.<sup>131</sup> If temporary symptomatic relief is obtained in this way, surgery may do good. The cold pressor test is another good method of judging the lability of the blood pressure. If, after bed rest of one or two weeks, blood pressure drops significantly, operation may be undertaken. If the nonprotein nitrogen is more than 45 mg. per 100 cc. of blood, sympathectomy is not indicated. If a patient can concentrate to 1.010 or more, his kidneys will tolerate the operation. In general, the younger the patient and the better the renal function, the better the probable outcome. If stroke is associated with the hypertension, *ventricular tap* may do good. This is especially true when increased intracranial pressure is revealed by marked papilledema.<sup>132</sup>

### Sulfonamides and the Kidneys

The sulfonamides are invaluable therapeutic agents when used against susceptible bacteria, but they must be used with extreme caution, as dangerous toxic reactions may occur. No body tissue is immune to sulfonamide toxicity, but their effects on the kidneys have attracted particularly wide attention.

Kidney reactions to the sulfonamides may be roughly divided into two groups,<sup>135</sup> the obstructive and nephrotoxic lesions. Obstructive damage is due to the extraneuphric precipitation of masses of sulfonamide in the kidney pelvis and ureters, or the intraneuphric deposition of crystals in the kidney substance itself. Direct nephrotoxic injury is not necessarily associated with obstruction, although both toxic and obstructive lesions may be found in the same kidney. Three types of toxic lesions have been recognized: (1) Simple tubular degeneration; (2) necrotic tubular degeneration; and (3) glomerular changes. These probably represent simply phases of one process and are not separate entities in themselves. Simple tubular degeneration is found in every case of sulfonamide renal damage, but in more advanced cases, tubular necrosis may also be seen. Glomerular changes are more rare, though they have been noted occasionally. Spink<sup>136</sup> states that sulfathiazole is most likely to cause renal complications, next sulfapyridine, and to a less extent sulfadiazine. Sulfanilamide is not apt to cause renal injury.

Continuous experimentation is being done to find a drug which will be bacteriostatically powerful and at the same time safer than the known chemotherapeutic agents. Taplin, Custer, and Young<sup>137</sup> report that when *sulfapyridine*, *sulfathiazole*, and *sulfadiazine* are not tolerated orally, their sodium salts may be given safely and conveniently by subcutaneous injection in concentrations of from 0.4 per cent to 0.8 per cent in isotonic solution of sodium chloride or  $\frac{1}{6}$  molar sodium lactate. When administering the drugs in this manner, dosage must be regulated on each individual by watching the blood levels of sulfonamide.

Laughlin, Bennett, Flanagan, and Spitz,<sup>138</sup> by studies on man relative to the absorption of the acid and sodium salts of sulfapyridine, sulfathiazole, and sulfadiazine as evidenced by blood levels obtained at short intervals during a three-hour period following administration, showed that these salts are rapidly absorbed from the gastrointestinal tract. The absorption of acid salts is increased by the simultaneous administration of an equal amount of *sodium bicarbonate*, but sodium salts are more rapidly and completely absorbed than acid salts given with or without bicarbonate. Conjugated forms were present in the blood as soon as five minutes after peroral administration of acid and sodium salts. When acid salts of sulfapyridine and sulfadiazine were given with bicarbonate, this effect was enhanced. When the acid salt of sulfathiazole was given with sodium bicarbonate there was less conjugation than when sulfathiazole was given alone. The average degree of conjugation was greater when the sodium salts of sulfapyridine, sulfathiazole, and sulfadiazine were given than when their respective acid salts alone or the acid salts with sodium bicarbonate were given.

It has been hoped that *sulfamerizine* may prove practical.<sup>139, 140, 141, 142, 143, 144, 145</sup> Murphy, Clark, and Flippin<sup>139</sup> found that after a single 3 Gm. (47 gr.) oral dose of sulfamerizine, higher blood serum levels were attained more rapidly and sustained longer than after similar amounts of sulfadiazine. Sodium sulfamerizine can be given intravenously or subcutaneously. Sulfamerizine is readily distributed throughout the body fluids and enters the red cells in varying concentrations. Its urinary excretion is slow and comparable to that of sulfadiazine. Its toxicity is no greater than that of other sulfonamides, but sulfonamide reactions have not been eliminated by the

use of this drug.<sup>140, 141, 142, 143, 144</sup> **Sulfamethazine**,<sup>146</sup> a heterocyclic derivative of sulfanilamide, has been reported by Rose and Martin to be safe even when given in large doses to mice. It is more soluble than sulfamerizine and sulfadiazine in acid urine, though sulfadiazine is more soluble in the alkaline range.<sup>147</sup> The activity of **sulfapyrazine** against infections with beta hemolytic streptococci was compared by Schmidt and Sesler<sup>148</sup> with that of sulfadiazine, sulfathiazole, sulfapyridine, and sulfanilamide. It seemed to be equal in effectiveness to sulfadiazine and superior to the other drugs. Higher blood concentrations were obtainable on smaller doses than with any of the other drugs studied except sulfadiazine. The blood level increased less with increase in dosage of sulfapyrazine than with any of the other drugs, and the concentrations were maintained at uniform levels longer. A later report by Ruegsegger, Brookens, Hamburger, and Grupen<sup>149</sup> on sulfapyrazine in pneumococcic pneumonia indicates that the drug is clinically effective, but that renal damage may occur.

Many reports of the mechanical and nephrotoxic renal lesions following sulfonamide therapy have appeared in the literature.<sup>33, 135, 150-159</sup> In addition to these, Press and Kennerstein<sup>160</sup> describe two cases of sulfathiazole toxicity unassociated with either calculi or anatomic changes. They feel the damage in these cases was due to a toxic reaction causing an alteration of function rather than structure of the nephron. Adams<sup>161</sup> describes cases in which a calcareous radiopaque membrane developed on the epithelial surfaces of the calices and renal pelvis when the kidney became partly or completely blocked by a ureteral calculus following the use of sulfathiazole and sulfadiazine. This type of complication is most likely to occur in the presence

of ureteral stasis, pyelonephritis, and alkaline urine. When drugs must be given in the presence of these conditions, the membrane may not form if ureteral stasis is corrected, ureteral drainage is maintained, urinary output is improved, and the urine is kept acid. The membranes should not be removed operatively at an early date, as spontaneous separation may occur later, making removal of the membrane easier. Or the membrane may be passed spontaneously. Luetscher and Blackman<sup>162</sup> report five cases of severe injury to the brain and kidneys in which a disturbance of sodium and chloride concentrations was at least partly responsible. Of the five patients, three died. The electrolyte disturbance occurred after the oliguria and anuria were relieved by adequate diuresis. This is explained by the authors as the result of excessive loss of water without adequate salt excretion. If salt is given with the fluids necessary to replace the water loss, the damage may be enhanced. They feel that such a specific functional disturbance must be associated with a specific renal lesion. They found such a lesion in two cases located in the intercalated segments of the distal convoluted tubules, the spiral portions of the proximal convoluted tubules, the collecting cortical tubules or the ascending limb of Henle's loop. In two cases the salt retention could not be correlated with any specific localized lesions.

Careful supervision may diminish the incidence of sulfonamide complications. Barnes and Kawaichi<sup>163</sup> list the chief factors influencing the formation of sulfonamide urinary concretions as: (1) Concentration of the drug in the urine, which may be reduced by decreasing the dosage and increasing the fluid intake; (2) the degree of acetylation, which cannot be influenced by extrinsic methods; (3) urinary stasis, overcome

by establishing and maintaining free drainage; (4) the  $pH$  of urine which may be adjusted; and (5) the temperature, which when elevated may increase the solubility of the drugs. Murphy and Wood<sup>33</sup> state that the kidney may be safeguarded by the following precautions: (1) Insurance of adequate hydration of the patient's tissues, and urinary intake and output. General opinion is that 1500 to 2000 cc. of fluid per day must be taken if adequate urinary output is to be assured; (2) evaluation of renal insufficiency or of obstructive uropathies before commencing sulfonamide therapy; (3) careful observations of the quantity of urine, the appearance on gross examination, and the microscopic examination for crystals. The presence of sulfonamide crystals does not mean that kidney damage is at hand, and that the drug must be stopped, but it does indicate that much care must be exercised concerning the quantity of the drug given, the optimal level in the blood stream and the volume of urine excreted; (4) alkalinization of the urine.

Although all do not agree on the value of alkalinization,<sup>164, 165</sup> this procedure has been advocated by many.<sup>33, 166-171</sup> Jensen and Fox<sup>170</sup> find that sulfathiazole and sulfadiazine solubility is minimal at  $pH$  5.6 to 6.6, is doubled or tripled at  $pH$  7.5 and increased 10 times at  $pH$  8.0. Peterson, Goodwin, and Finland<sup>172</sup> observed the effect of a number of commonly used procedures on the urinary excretion of sulfadiazine. They found that the greatest and most prolonged increase in excretion occurred when the drug was given with sodium bicarbonate in amounts sufficient to make the urine highly alkaline. The drug in the urine became less concentrated most rapidly after intravenous injection of a large quantity of 5 or 10 per cent *glucose solution* in distilled water. Water and

physiological saline produced the same result, but not so quickly. Only the first of these three procedures was accompanied by a large increase in drug output. These authors suggest the clinical application of these findings. When, as in sulfadiazine reaction, it is necessary to eliminate the drug rapidly, alkalinization of the urine is useful. If the maintenance of high levels is desired, the urine should be kept acid, a method which is likely to be safer than increasing the oral dose, supplementing the oral dose by parenteral administration, or by limiting the fluid intake. If renal complications are present, the urinary output should be increased by large amounts of 5 or 10 per cent glucose in distilled water or, if this is not possible, by the ingestion of large quantities of water.

Luetscher and Blackman<sup>162</sup> suggest that attention to the electrolyte concentration of the blood may be beneficial, as a hyperchloremia may enhance the damage done. In cases of hyperchloremia, the addition of salt with fluid administration is dangerous. Lehr<sup>167</sup> also found that although fluids should be given in conjunction with sulfonamides, sodium chloride is apt to increase any resultant damage. He recommends that measures be taken to insure against high sodium chloride concentrations in the body during sulfadiazine treatment and advises caution, especially in the use of infusions of physiological saline. He adds that forcing of water or fluid is better than no treatment, but once full obstruction has developed, the continued administration of fluid may lead to water intoxication.

The importance of controlling the blood level has been emphasized by many, and a level over 12 mg. per cent is considered dangerous.<sup>151</sup> Heinemann,<sup>173</sup> after studying the distribution of sulfanilamide, sulfathiazole, sulfapyridine, and sulfadiazine compounds between cells

and serum, felt that determinations of the blood levels should be done on plasma or serum, rather than whole blood. Of the four compounds investigated, only sulfanilamide was more concentrated in the cells than in serum and sulfathiazole was most highly concentrated in serum. Transfer of these compounds occurs in certain conditions from cells to serum and back. Some authors find that blood levels and dosage are not the deciding factors in kidney damage from sulfonamides.<sup>135</sup>

Tests have been devised by which the urinary concentration of sulfonamides may be determined quickly and easily. It is thought that these may help prevent untoward reactions. Kawaichi<sup>174</sup> states that if the urinary concentration of sulfonamide is less than 100 mg. per cent and acidity and temperature are normal, concretions will not form. If it is above that, it will be possible for concretions to occur. A simple test applicable to sulfapyridine, sulfathiazole, and sulfadiazine was described by him for determining whether or not the concentration is over 100 mg. per cent. Five cc. of urine at room temperature are put in a test tube and 10 drops of concentrated hydrochloric acid are added. The contents of the tube are shaken, and a small piece of wood fiber paper is put in. The contents are shaken again. In six minutes, if the paper has turned yellow, the concentration is less than 100 mg. per cent; but, if it is orange, the concentration is higher. Rag fiber paper cannot be used in this test. Bogen<sup>175</sup> reports a test similar to that of Kawaichi. Lehr and Churg<sup>176</sup> put 15 ml. of a reagent containing a 2 per cent solution of dimethylparaaminobenzaldehyde in ethyl alcohol and a 3 per cent aqueous solution of trichloroacetic acid in proportion of 1:2, into a test tube and add one drop of urine. If there is 1 mg. per cent of free

sulfonamide or more in the urine, bright yellow streaks form. For quantitative analysis, the contents are mixed and part is compared to a permanent standard. This test can also be done with filter paper dipped first into the reagent and then into urine. Free sulfonamide turns the paper a deep yellow or orange.

The use of *liver extract* seems to reduce sulfonamide toxicity in rats without destroying its effectiveness.<sup>177</sup> This is interesting in view of the fact that liver damage has been thought to bear a relationship to the renal injury resulting from sulfonamides.

Sobin, Aronberg, and Rolnick<sup>178</sup> found that *urea* given simultaneously with *sodium acetylsulfapyridine* prevented pathologic changes in the kidneys by preventing the precipitation of the drug and formation of renal calculi in rats. This is not due to the diuretic effect of urea, but to its solvent action on acetylsulfapyridine.

Impending toxicity is heralded by dropping of the fluid output to below 1000 cc., elevation of the nonprotein nitrogen and microscopic hematuria. When sulfonamide toxicity is diagnosed, the drug should be stopped immediately, fluids should be forced, and restorative therapy instituted. In the presence of anuria, cystoscopy and catheterization are indicated, and the pelvis should be washed often with warm alkaline solutions. In resistant sulfonamide injury, when medical methods have failed, decapsulation of the kidneys may result in a cure. Excellent results following decapsulation have been reported by Weinstein and Adams,<sup>180</sup> Wattenberg and Coleman,<sup>179</sup> and Murphy, Kuzma, Polley, and Grill.<sup>135</sup> When the pelvis or ureters are blocked, free renal drainage may be established by pyelostomy, ureterostomy, or combined pyeloureterostomy, according to Campbell and Fobes.<sup>181</sup>



### Crush Injury

The syndrome of renal failure following crushing injury to the muscles has continued to excite interest during the past year. This condition is an important one, since modern warfare and the bombing of cities have made such injuries common.

Bywaters, cited by Bradley,<sup>188</sup> who has written an excellent review of the subject, states that usually the patient is pinned under debris for several hours before release. He appears to be well at first, except for wounds, fractures, and the condition of the compressed limb, which is pale, cold, and pulseless, with some degree of paralysis. Soon, however, shock appears, and is evidenced by pallor, sweating, hemoconcentration, and hypotension, and the limb becomes tense and swollen. Bywaters states that this shock is due to loss of plasma through the damaged capillary walls into the injured extremity. The body attempts to compensate for the decrease in blood volume by vasoconstriction, but when this is no longer possible, the blood pressure drops and shock is established. Tomb<sup>182, 187</sup> feels rather that this shock is incited by overstimulation of the sympathetic nervous system, which causes dilatation of the capillaries of the skeletal muscles and constriction of those of the skin and abdomen. This results in primary shock if the stimulation is severe enough, but if not, the effect is cumulative and shock appears later. The capillary dilatation, hypotension, and absence of muscular activity lead to capillary stasis. This is in time followed by asphyxiation of the capillary endothelium from oxygen want, exudation of plasma, and loss of blood volume. Pain, fear, cold, anxiety, hemorrhage, sweating, and vomiting aggravate the syndrome. Administrations of fluids such as serum,

citrated plasma, or blood intravenously will control this shock.

The patient appears to do well until urinary symptoms, as hematuria and acid urine, albuminuria, creatinuria, pigmented granular casts, and oliguria set in. The urine remains dilute despite the oliguria. The pigment, as a rule, is not found after the second day. The limb continues to swell. It becomes hard, and the skin may show petechial hemorrhage, erythematous wheals, and blisters. There is limb anesthesia and paralysis and often absence of arterial pulsation. Gangrene may set in. The patient is at times apathetic and anxious and may be subject to vomiting. Blood pressure rises; the carbon dioxide combining power of plasma falls; the urinary output diminishes; urea concentration and the power to absorb chloride is impaired; and severe loin or abdominal pain and rigidity develop. At the critical period, which occurs about a week after the onset, there may be a sudden diuresis and recovery, or the oliguria may progress to anuria with subsequent uremic death. When death occurs, it is usually sudden. In serious cases, cardiac irregularity may come on and the electrocardiograph shows changes similar to those taken after potassium poisoning. The serum potassium is increased, which may cause the toxic effects. Insulin injections may be valuable in restoring the potassium values to normal.

At autopsy the kidneys appear congested, pale, and edematous. The chief gross and microscopic changes occur in the tubules, and the glomeruli are apparently not much affected. The distal tubules and collecting ducts are filled with brown granular casts which sometimes pass through the damaged tubular wall into the interstitial space. These casts may be composed of desquamated epithelial cells, hemoglobin, myohemoglo-

bin, or bile pigment. The distal segments of the renal tubules may be severely damaged, and the changes vary from cloudy degeneration to necrosis and rupture of the tubular wall. The injured muscle is pale, with some hemorrhage into it, and the muscular tissue is necrosed. Changes may also be found in the adrenals, blood vessels, and skin. There may be traumatic lesions as fat embolism, contusion, or blast lung.

The etiology of this syndrome is the subject of much discussion and is a matter on which few agree. It is becoming evident, however, that this type of renal damage resembles that of blackwater fever, transfusion reaction, hemolytic anemia from sulfonamide therapy, myohemoglobinemia, and favism.<sup>183</sup> Crush injury is related to burn and blast injuries, according to Lee,<sup>184</sup> who states that these three conditions have two common etiological factors: (1) The loss or escape of plasma from the circulating blood stream; and (2) toxemia due to degenerative changes and products liberated from dead and dying cells, plasma and bacteria.

The cause of this syndrome has been attributed to flooding of the body by poisons of dead and dying tissues after pressure on the body is removed.<sup>184</sup> Many feel that this poison is due to products of hemoglobin.<sup>185</sup> Bing<sup>186</sup> infused crystalline methemoglobin into dogs acidified with ammonium chloride, and noted that there followed a fall of effective renal plasma flow and glomerular filtration rate, with death ensuing in some cases within three days. Infusions of metmyoglobin and hemoglobin into acidified animals and of methemoglobin and hemoglobin into normal animals did not adversely affect renal function. The renal lesions in acidified dogs given methemoglobin resemble those due to crush syndrome. Some state that the

deposition of hemoglobin products in the tubules results in obstruction with oliguria and anuria coming on as a result. Bywaters<sup>188</sup> states that myohemoglobin is released by the injured muscle and deposited as acid hematin in the kidney in the presence of acid urine. He reports that experimentally in rabbits whose muscles contain no hemoglobin, muscle necrosis causes a condition similar to crush injury except that there is no myohemoglobinuria or renal failure. When myohemoglobin in quantities comparable to that excreted in human crush injury was injected into rabbits acidified with ammonium chloride, death from renal failure followed. This author feels, however, that the proof of this theory will lie in the success of alkali therapy in preventing renal failure.

Other writers feel that the syndrome of renal failure in crush injury depends on dehydration, diminished blood volume, renal circulation, and glomerular filtration, and that the azotemia is extra-renal in origin.<sup>188</sup> The blockage is secondary to the anuria, though when it occurs it aggravates the renal failure. Disturbance in the acid-base-electrolyte-water balance may be instrumental in the kidney insufficiency. Anderson<sup>185</sup> suggests a vascular mechanism as a possibility. Tomb,<sup>187</sup> as indicated before, would consider anoxia due to traumatic shock as the seat of the trouble. He disproves the theory that the syndrome is due to toxic materials from crushed or necrotic muscle by pointing out that the renal damage is early in appearance and progressive, even when a limb is amputated, and that it has not been proved that the blood of crushed animals is toxic. Also this type of injury is not found after infarction or absorption of a blood clot and it may occur where no crushing of muscles has occurred. The wide divergence of opinion on the subject of the

etiology of crush syndrome would indicate that probably no one factor can satisfactorily explain this complex condition.<sup>189</sup>

Bywaters cautions against confusing this clinical entity with oliguria from oligemic shock alone, dehydration due to vomiting or inadequate fluid intake, blockage from sulfapyridine crystals or transfusion reaction. Examination of the urine, blood, determination of the blood pressure and an intake chart will aid the diagnosis. Oliguria may result from cortical necrosis after traumatic injury to the liver with necrosis. Passage of a catheter will reveal the true diagnosis. Hematuria from direct injury and hemoglobinuria from exposure to cold may be differentiated by examination of the urine and the use of the spectroscope. Limb swelling may be due to hematoma, but if it is, wheals typical of crush syndrome are absent, and the muscle does not feel doughy.

The prognosis depends on the extent of injury, degree of hemoconcentration, oliguria, and blood urea rise.

The patient will recover from the initial shock following the usual procedures, provided his blood pressure has not been allowed to remain below 80 mg. Hg. for too long. The main problem is control of the oliguria.<sup>190</sup> Diuretics do no good, nor do hot packs, according to Buerman. Intravenous fluids may be dangerous, especially when given in large quantities or too quickly, and they should be discontinued or given by the drip method if they do not induce diuresis. *Milking the limb* by applying intermittent pressure to force the plasma out into circulation in combination with plasma therapy has done good.

The value of *alkalinization* has been questioned by some, but it has been followed by good results in many cases. Bywaters recommends treatment of the

renal damage first, then the shock and finally the limb condition. Ample alkaline fluid should be given, according to him, for alkaline diuresis, if possible, while the patient is still crushed. *Morphine* may be necessary, and *coffee or tea* are beneficial. In alkalinization, potassium salts should not be used, as serum potassium may be already elevated. With the kidneys thus protected, *plasma or serum* should be given to combat the shock and restore circulation. A large quantity may be needed. Saline is useless and overheating the patient is to be avoided. In the therapy of shock, *adrenal cortical extract* has been used, but some feel it may be harmful and that it can initiate a syndrome identical to shock. *Paredrine*, a vasopressor, is useless when shock is brought on by escape of plasma fluid, as it seems to increase the loss of fluid through the capillaries, whose permeability is impaired. Tomb advises *ergotoxin* to relax the capillaries of the skin and abdomen and prevent the anoxia. When the shock is under control, attention may be directed to the limb condition. If amputation is necessary, it should be done early to prevent the absorption of autolytic products. A tourniquet may be valuable. In the later stages, *amputation* should be done only if the limb is nonviable. Provided there is ample alkaline diuresis, circulation to the limb may be restored by various measures as *elevation of the leg, incision of fascial sheaths, stripping of the damaged artery*, or the use of *alternate positive and negative pressure*. Vasodilatation is best achieved by *alcohol* and warming of the body. The limb itself should be kept cold rather than hot.

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## DISEASES OF METABOLISM

JOSEPH T. BEARDWOOD, JR., M.D., and GEORGE P. ROUSE, JR., M.D.

### Food Rationing

Despite the dietetic restrictions imperative during the past year of war, diabetic patients have fared well. As a whole, local rationing boards throughout the state and country have been most co-operative in allowing these patients extra protein and fat, and in some cases have even given processed foods, particularly fruits and fruit juices, when such fresh products were limited. As a rule, with the exception of rare cases, it has been found necessary to ask only for fats and protein.

Early in the war, the English government appointed a committee to go over the rationing system with particular attention to invalids and diabetics. At that time, it was perfectly obvious to them that patients not taking insulin could not substitute more of the carbohydrate food for the restricted protein and fat. As a matter of fact, those patients on an insulin régime could increase their insulin dosage as required to allow for the increased carbohydrate made necessary because of the protein and fat shortages. However, no distinction was made between the two groups and it was decided that all diabetic patients giving up their sugar allotment could obtain extra protein and meat upon recommendation of their physician.

Shortly after the onset of war in this country, there were so many unjustifiable demands on the part of some physicians, in regard to the amount of food necessary to maintain the diabetic patient, that local rationing boards in some districts were somewhat reluctant to meet a reasonable request. As the past year has progressed, the rationing system of diabetics has been working quite satisfactorily, and at the present time legiti-

mate demands are being met. The problem of rationing the diabetic has been concerned primarily with the protein and fat foods which, during the past year, at some times has been acute, with the meat and butter shortages.

Most diabetic diets have a generous amount of protein and, since butter and cheese are also included under our rationing system, it becomes perfectly obvious that allowances of these foodstuffs must be made. Many diets were found to be too high in fat to permit, from a practical standpoint, as much substitution as was necessary with the present allowances. As a rule, it was found that a person needs approximately three pounds of meat and one pound of butter per week.

There has been considerable controversy as to whether extra allowances should be made for canned carbohydrate foods such as fruits and fruit juices. Unfortunately, there have been times when vegetables and fruits, especially oranges, have been not only scarce but prohibitive in cost. As a result, many of the poor patients were unable to procure them. It is felt that, in general, it is unnecessary to ask for extra point allowances for this type of food, and but for the rare, exceptional case it has not been done. Patients are encouraged to use as many fresh fruits and vegetables as possible, as many are cheaper and certainly more nutritious. Many patients, during the spring and summer months, have planted a victory garden and have not only obtained the desired vegetables, but certainly have been benefited by the exercise obtained. Patients have also been encouraged to use more milk and cream, as these are not rationed and certainly are sources of protein. Eggs



also are unrationed and an economical source of protein. Fowl and fish have also been suggested as containing protein.

In certain states, such as Indiana, the State Medical Association<sup>1</sup> has cooperated with the O.P.A. in establishing lists in which maximal amounts of food necessary for certain special diets are listed. They emphasized the necessity of expressing in dozens, pints, quarts, or pounds the amount of food necessary rather than in ration points, as there is considerable variation from time to time of the point value of certain foods.

### Glycosuria

The presence of sugar in the urine of a patient should always cause the physician to consider that patient as a diabetic until proven otherwise. There are a number of other conditions which may cause glycosuria other than diabetes mellitus, but since this disease is the most common cause and since, likewise, so much can be done for the present-day diabetic, it is imperative that the cause of this glycosuria be immediately ascertained. When the urine contains a large amount of sugar and the patient has the classical symptoms in addition to an abnormally high fasting blood sugar, there is no question as to the cause. Unfortunately, it is not as easy as this in all cases, and at times it is difficult to be certain of the etiology. After sugar is found in the urine, a patient should have a fasting blood sugar done, and if this blood sugar is over 150 there can be no question of a true diabetes. With a fasting blood sugar above 120 and below 150, without any symptoms of diabetes being present, or family history of same, it has been the practice to do a three-hour glucose tolerance test. Whatever the reason, it has been pointed out recently by Dewees and Langner,<sup>2</sup> and seems to be a fact, that when conclusions are drawn from a

single glucose tolerance test, an individual with apparently nondiabetic glycosuria is more likely to develop diabetes than a normal individual. Such has also been the experience of workers in the Joslin clinic. Dewees and Langner report that in a series of 37 individuals with apparently nondiabetic glycosurias based upon one glucose tolerance curve obtained 5 to 13 years ago, a greater number developed diabetes than can be accounted for on the basis of chance. It is their opinion that the amount of glucose in the urine was of itself of no great prognostic significance.

Another cause of nondiabetic glycosuria is the so-called "renal diabetes" or better, renal glycosuria. This is a condition in which glucose is excreted in the presence, however, of a low blood sugar level; this spilling is due to a low renal threshold. The diagnosis of renal glycosuria should be made only when the renal threshold is quite low, which is indicated by the finding of sugar in the urine at all times during the day, including an overnight fast. This condition, in the past, has been thought to be very infrequent. Although some workers in the field contend that renal diabetes never progresses to a true diabetes, the authors saw two such cases personally which had a renal glycosuria and later developed diabetes mellitus with its accompanying symptoms. In this regard, the work of Blotner and Hyde,<sup>3</sup> who studied renal glycosuria in selectees is of interest. They found 33 cases of renal glycosuria, proven by sugar tolerance test, in 367 consecutive patients with glycosuria between the ages of 18 and 45 years. This is in sharp contrast with the low incidence previously reported in other clinics. Renal glycosuria occurred in the younger selectees; 23 were between the ages of 20 and 29 years of age, while 10 were 31 to 44 years of age. Of interest also was the

fact that in approximately one-third of the cases, a family history of diabetes was obtained. In none of these cases were there any symptoms of diabetes. The average heights were normal and in all but two cases the weights were normal or subnormal. It is of importance in cases of glycosuria to differentiate the renal glycosurias from the diabetics; in the former there is no specific treatment, only periodic observation, while in the latter, careful and continuous control of their diabetes is of utmost importance.

Recent studies by Mirsky and Nelson<sup>4</sup> in renal physiology have revealed information which should help greatly in determining the real significance of glycosuria. This information involved the Cushny filtration-reabsorption theory of renal function, and the application of newer principles to the problem of dextrose excretion. It has now been shown that the crystalloids of blood are filtered into the tubules by the glomeruli where either they are reabsorbed or concentrated and subsequently excreted. As a result, dextrose excretion is dependent on: (1) Its concentration in the arterial blood supplying the glomeruli; (2) the rapidity in which it is filtered out of the blood by the glomeruli, and (3) the rate which it is reabsorbed by the tubules. Mirsky goes on to point out that very commonly the elderly diabetic has a high blood sugar level without any marked glycosuria, comparable to that seen in a younger patient with diabetes with a "decreased renal threshold." As a matter of fact, the same patient may show more sugar in his urine in spite of a high blood sugar level. This is now explained on the basis of decreased glycosuria due either in part, or entirely, to a decrease in the glomerular filtration proportionate to pathological changes in the glomeruli or to an increase in the capacity to reabsorb glucose.

For these reasons Mirsky feels that the amount of sugar in the urine alone is not proportionate to the severity of the metabolic disturbance present, nor is it of any value in respect to the prognosis. He feels that only when the renal factors are properly evaluated is the amount of sugar in the urine of significance. From this, one is able to find out the amount of carbohydrate retained on a measured intake and arrive at a proper evaluation of the severity of the diabetic state.

In addition to the above mentioned causes of glycosuria there are many states in which a transitory glycosuria is often found. Sugar is often found in the urine of pregnant or parturient women. It should never be forgotten, however, that diabetes mellitus may have its origin during pregnancy or that a known diabetic may become pregnant. Glycosuria often accompanies disturbances of the endocrine glands, the most common type probably is that found with hyperthyroidism. Again one must remember that the two diseases may occur together and when present the necessary procedures must be taken. Likewise, it is found quite often in lesions of the pituitary gland, particularly acromegaly. The association of glycosuria with disease of the anterior pituitary gland has received considerable investigation in recent years especially after the work of Houssay, Young, and others. Transitory glycosuria of intracranial origin was demonstrated in the classic experiments of Claude Bernard in which the puncture of the floor of the fourth ventricle in animals caused transitory glycosuria. It has long been known that in a certain percentage of head injuries, sugar is found in the urine for a limited time. Infections and toxemias, likewise, give rise to glycosurias, as do certain chemical agents. Probably the most common of these is ether or chloroform anesthesia. This has

been thought due partially, at least, to acidosis produced by the anesthesia, as, years ago, it was shown that the carbon-dioxide combining power decreased with the corresponding increase in the blood sugar during this state. Despite the many causes numerated above, as well as others giving rise to sugar in the urine, it is still felt that from a practical point of view it is wise to consider glycosuria as diabetic in origin until steps have been taken to prove it otherwise. In the absence of other definite disease entities, it is most desirous to do a glucose tolerance test in helping to evaluate the glycosuria, provided, of course, that the fasting blood sugar is not over 150 mg. per cent.

### **Treatment of Diabetes Mellitus Without Regard to Hyperglycemia and Glycosuria**

As a result of his work in the Out-Patient Department of the New York Hospital, Tolstoi<sup>5</sup> has again presented his criteria for the satisfactory treatment of diabetes mellitus using protamine zinc insulin. He feels that the basic principle is the quantity of glucose utilized and not excreted, and cites the evidences of such utilization as maintenance of optimal weight, absence of diabetic symptoms, and absence of ketonuria. He believes that complications attributed to hyperglycemia and glycosuria are inferential and inconclusive. As a result, in the handling of his patients, he does not insist on a normal blood sugar without sugar in the urine, and feels that in his experience such criteria are unnecessary in the control of this disease. He goes on to state that these patients develop no more frequent or severe infections than those more rigidly controlled, and when surgical procedures were performed on them, their wound healing was consistent with that of the nondiabetic. Of interest

is his feeling that when one attempted to control the diabetes more rigidly, namely, keep the blood sugar within normal limits and the urine sugar-free, unpredictable and sometimes severe reactions occurred which was not the case in the other groups of patients studied.

In a paper recently published by Henry John<sup>6</sup> he states that the above views of Tolstoi regarding glycosuria are completely opposed to all the work done in this field in the past 30 years. He points out that a heavy glycosuria means a marked hyperglycemia for the greater part of the day. These patients often start out in the morning with a low blood sugar, but have a high blood sugar for the rest of the 24-hour period. Again he emphasizes that the actual quantity of sugar excreted depends on the height of the renal threshold for sugar and the length of hyperglycemia. As has been frequently pointed out, diabetic patients who have been diabetic for years often show a high renal threshold, so that even in the presence of a high blood sugar, only a small amount of sugar may be excreted by the urine. He feels that hyperglycemia has a deleterious effect on the diabetic state which becomes progressive, and results in a more severe diabetic state.

From experience, many clinicians interested in diabetes have found that early, adequate, and continuous control of diabetes results in a milder type of the disease, and certainly, as a whole, this principle should be followed. There is no doubt that some diabetics cannot be kept sugar free on protamine zinc insulin without severe hypoglycemic reactions. Many men feel that one is justified in permitting this group of patients to spill small amounts of sugar at times during the 24-hour period, although the amount spilled is not enough to affect maintenance of body weight or produce acidosis

or an increase in the diabetic symptoms. The authors do not feel that the patient should be put on an unrestricted diet and be given arbitrary amounts of protamine zinc insulin without regard to the resulting glycosuria. In this group of patients it has been the custom to use combinations of protamine zinc and regular insulin. Due to the action of the regular insulin, this combination usually prevents the initial marked rise which one experiences with protamine zinc insulin alone, and at the same time tends to keep the blood sugar within normal limits during the 24-hour period without hypoglycemic reactions occurring. About 25 per cent of the patients seen, particularly the juvenile diabetics, belong to a group known as severe or labile diabetics, who require multiple doses of regular insulin daily to maintain control. If these people are given protamine zinc insulin alone they will either spill sugar and not be in proper control, or else they will have severe reactions. Again it seems wise, in this type of case, to add unmodified or regular insulin to the protamine zinc insulin, and by so doing the control is much more adequate.

Proper control of diabetes, in the writers' opinion, as in that of most workers in this field, is of paramount importance. As a result, it is generally felt that one should attempt to keep the blood sugar in diabetic patients as close to normal limits as can be attained, and attempt likewise to keep the urine sugar free as long a portion of the day as is possible. For this proper control of any diabetic, one must rely on routine blood sugar studies, as well as occasional fractional urinalysis, so that the dose of insulin may be distributed at the proper times adequately. Unless such procedures are undertaken to control one's diabetics properly, the physician has not

completely fulfilled his obligation to the patient.

### Insulin

During the past year, considerable work has been done at a number of clinics in respect to the mixing of protamine zinc with regular insulin to be administered at a single injection, usually before breakfast. As has been stated previously, the principal aims in the control of diabetes are to maintain a blood sugar throughout the 24-hour period which is for all practical purposes almost within normal limits, to keep the urine sugar free, to maintain body weight, and to avoid accentuation of the cardinal diabetic symptoms, but at the same time, to prevent the occurrence of severe hypoglycemic reactions. Practically, one attempts to maintain the level of the blood sugar throughout the day within reasonable variations of normal. It has been found generally, in all cases, that a single injection of protamine zinc insulin, as a rule, will maintain satisfactory control in the mild diabetic. This is true only of the mild diabetic, however, and adequate regulation of the moderate, severe, or labile diabetic, in almost all instances, requires multiple daily injections of various types of insulin. One of the great disadvantages with protamine zinc insulin alone, given in the morning, has been the morning lag with markedly elevated postprandial blood sugar levels. In order to eliminate the mid-morning lag in insulin action, with consequent heavy glycosuria during that part of the day a number of investigators have attempted mixtures of protamine zinc and unmodified insulin in varying ratios given together in the morning. Colwell and Izzo<sup>7</sup> have used mixtures containing one-third of the protamine zinc and two-thirds of the regular insulin. Others, such as Rynearson and Hildebrand,<sup>8</sup> have em-

ployed ratios of protamine zinc to unmodified insulin between the two extremes of 1:1 and 1:5. They felt that the use of the two insulins in these varying proportions were capable of adequate control of the blood sugar during the 24-hour period. They pointed out that injection of the two types of insulin at separate sites would not give a satisfactory control of the blood sugar level during the 24 hours, as would their injection together. One disadvantage following their injection in separate sites was a marked hypoglycemic effect. Peck<sup>9</sup> believes that the technic of instituting treatment of the uncomplicated case with regular insulin and protamine zinc insulin does not differ from the generally previously accepted procedures. The dose of protamine zinc insulin is increased gradually until the fasting sugar in the morning approaches normal. As this dose is further increased, hypoglycemic shocks during the night are frequently encountered. If postprandial blood sugars taken at 11:00 A. M. and 3:00 P. M. are excessively high it is obvious that regular insulin is needed during the daytime. Readjustment of doses depends on two factors, namely, the fasting blood sugar before breakfast serves to indicate the dose of protamine zinc insulin necessary and postprandial blood sugars indicate the necessary dose of regular insulin. He feels that the proper ratio of combining protamine zinc and regular insulin together varies with different individuals and that the mixture must be adjusted using the criteria as mentioned above.

MacBryde and Roberts<sup>10</sup> have reported a series extending over three years and have concluded that a single injection of protamine zinc insulin established adequate regulation only in the mild diabetic. They felt that the proportion most useful in the majority of cases was three parts of protamine zinc to

one part of regular insulin. Sparks and John<sup>11</sup> feel that practically all diabetics can be adequately controlled on this mixture given once a day, and in 150 cases which they studied, only three cases could not be adequately controlled by the one injection régime.

The technic used by Sparks and John is as follows: Each morning at injection time regular insulin is taken into the syringe first in the proper amount and this is followed by the taking in of the proper amount of protamine zinc insulin. The injection is immediately given. The regular insulin is taken into the syringe first so that no protamine zinc insulin can be introduced into the regular insulin bottle. They feel that this is more satisfactory than the use of stock solutions of fixed proportions; it has the added advantage that it can be adjusted to meet the individual needs. They again emphasize the importance that the only criteria as to the relative amounts needed is the level of the fasting and postprandial blood sugars. The juvenile diabetics, in their opinion, are the ones who have benefited most from these mixtures.

### Globin Insulin

During the past year, globin insulin with zinc has been released to the public by one of the manufacturers. As yet, there is much work to be done on this type of insulin, although to date there have been a number of clinical reports. It is a clear, almost colorless, aqueous solution containing insulin modified by the action of purified globin, derived from the hemoglobin of beef blood, and zinc, in the form of zinc chloride. It is said to be quite stable and it has been stated by the manufacturers that no noticeable change in either potency or duration of action has been found after refrigeration for over two years.

**Action**—Theoretically, the action of this type of insulin is intermediate between regular insulin and protamine zinc insulin. Globin insulin does not exert its hypoglycemic effect as rapidly as regular insulin, but there is some hypoglycemic effect apparent within two hours after its injection. Its action is said to increase rapidly and the maximum effect extends from the eighth to the sixteenth hour. Its action then markedly diminishes and at the end of the 24-hour period there is said to be no action whatsoever remaining, as a result of which there is no accumulative action as is the case with protamine zinc insulin. Consequently, it would seem that this type of insulin, if given in the morning, has its maximum action during the day and its minimum at night. Theoretically, this is an ideal situation as it parallels the physiologic needs of most patients. Actually, in a limited number of cases, it has been the authors' experience as well as that of others, that such is not always the case. Dietary adjustments are sometimes necessary, as the distribution of carbohydrates must coincide with the intensity of the insulin action. Bailey and Marble<sup>12</sup> recommend that it be injected 30 to 60 minutes before breakfast and find that if such is done, there is less tendency to postprandial hyperglycemia. It must be emphasized particularly to the patient, as well as to the physician, that because of its prolonged and relatively intense action, hypoglycemic reactions may develop gradually much as they do with protamine zinc insulin, in contrast to the sudden, abrupt reactions experienced with the use of regular insulin.

Regarding dosage, Barnes and Duncan, and others who have worked with it, have felt that the total amount of globin insulin required is less than that of protamine zinc or regular insulin. This has been attributed to its effective

action during the day when the physiologic needs are greater and lessened activity during the night when the needs are not generally as great. It is usually given to most patients with a single injection, although a few of the more severe cases, particularly the juvenile cases, may require morning and evening doses. Mosenthal<sup>13</sup> and others have used it in conjunction with protamine zinc insulin in the control of certain severe cases and feel that this regimen has worked out quite satisfactorily. When such a combination is used, both the globin and protamine zinc insulin are given in the morning before breakfast, as separate injections. Adequate globin insulin is given to control the patient during the day and protamine zinc insulin is given in sufficient dosage to control the patient during the night.

In view of the work of Barnes and Duncan, Marks, Andrews and Groat, and Bailey and Marble, one must conclude that globin insulin is a long-acting insulin with the duration of activity shorter than that of protamine zinc insulin, but certainly longer than that of regular insulin. From experience, it is not felt, at the present time, that it has significant advantages in the control of diabetes that cannot be found with the proper use of protamine zinc insulin in combination with the various unmodified insulins.

### Cholesterol

During the past year Cook<sup>14</sup> has reviewed very carefully the metabolism of this substance. In brief, he finds it a constituent of all cells, although as yet its definite metabolic function has not been ascertained. He suggests that it is important in the maintenance of the cell, and likewise, most likely is very important as a medium for the transportation of fatty acids.

Leiboff<sup>15</sup> has described recently a simple and accurate test for the determination of total cholesterol and cholesterol esters in the blood. After doing more than 400 determinations by this method, he finds that the average total cholesterol in normal blood was 180 mg. and the average cholesterol-ester content was about 65 mg. per 100 cc.

Cholesterol can be deposited from the bile to assist in the formation of gallstones; likewise from the intimal coating of the arteries to produce atheroma. LeWinn and Zugerman,<sup>16</sup> studying fat metabolism in acne vulgaris, feel that cholesterol is chemically related to the steroidal hormones, as well as being intimately associated with the metabolism of fats. The relationship of these processes to the metabolism of cholesterol and to the dietary cholesterol remains, as yet, not clear.

Hirsch and Weinhouse<sup>17</sup> have recently reported on the rôle of lipids in atherosclerosis, and feel that the fatty deposits with atherosclerosis have the same lipid composition as the blood plasma and normal intima. This strongly supports the fact that lipid deposits in this process are the result of a known selective deposition of the plasma lipids. Even though cholesterolemia may favor the development of atherosclerosis these changes develop in adult life without significant elevation of the blood cholesterol level or other detectable abnormality of the blood lipids. The calcification occurring late in these lesions is probably identical with that which develops in any necrotic or devitalized tissue of the body. They conclude that the evidence which they have presented suggests that an atherosclerosis develops from disturbances in lipid metabolism as a result of which the latter infiltrates into the tissues of the intima. Just what the nature of these disturbances and the exact interactions, conver-

sions, and mechanisms are, at the present time, is not obvious. Not only these authors, but most other investigators, feel that abnormalities of fat metabolism, particularly that associated with uncontrolled diabetes in which the blood cholesterol level is elevated, certainly not only predisposes toward but accelerates the development of these changes in the intimal lining of the artery. For that reason, in controlling the elderly diabetic, it has been made a point to include only a moderate amount of fat in the diet; from time to time blood cholesterol determinations should be made.

### Diethylstilbestrol

In the 1943 SERVICE VOLUME, the authors reported results with the use of *diethylstilbestrol* in the treatment of diabetes mellitus. This study was covered in some detail and consequently it will not be reiterated. During the past year, several papers have come out both from the experimental and clinical aspects. Allen and Bern<sup>18</sup> have shown that the oral administration of this substance to guinea pigs of both sexes causes definite enlargement of the adrenal cortex. Janes and Nelson,<sup>19</sup> on the basis of experiments reported, have attempted to formulate a theory explaining the mechanism whereby diethylstilbestrol raises the levels of carbohydrates in the rat. They feel that since the substance is effective in adrenalectomized or hypophysectomized animals, it is apparent that each of these glands must be involved in the mechanism. Thus, diethylstilbestrol probably stimulates the hypophysis to release some factor, most likely the adrenotropic hormone, which in turn stimulates the adrenal cortex to produce some cortical hormone or hormones which are effective in promoting glyconeogenesis and the deposition of glycogen in the livers of fasting animals. Gitlow and Kurschner<sup>20</sup>



have studied this drug clinically in four groups of patients:

1. Those with a coincidental onset of diabetes in the menopause.
2. Those whose diabetes was aggravated by the menopause.
3. Those whose diabetes occurred long after the menopause.
4. Those with no menopausal symptoms and presumptive allergic conditions preventing the use of insulin.

They agreed with the findings of Mazzer and Israel as well as with Beardwood and Rouse<sup>21</sup> that patients whose concomitant diabetes and the menopause all responded favorably to *estrogen*, as well as those patients with aggravation of their diabetes at the time of the menopause. They also concurred with the work done by the previous mentioned workers that the response was the same with *ertrone* (ketohydroxyestrin) and with *estradiol benzoate* (dihydroxyestrin benzoate), provided large enough doses were administered. They pointed out that subjective improvement was always accompanied by marked reduction of glycosuria and hyperglycemia, and that the urine often became sugar free. This again was similar to the results obtained by Beardwood and Rouse, who found that one of the great advantages of this drug, in any age group, was its tendency to make the labile diabetic more stable. It was their opinion that diethylstilbestrol was most effective in patients in whom diabetes developed at about the same time as the menopause, or those with aggravation of their diabetes at this particular period of life.

As yet, there has been a scarcity of clinical work done on this particular subject, and in time, no doubt, more definite data and opinions will result. It certainly cannot be used as a substitute for insulin.

### Insulin Resistance and Infection

Previously, the widely accepted theory of insulin resistance was that there was a decrease of endogenous insulin secreted by the pancreas. In a paper by Greene, David, and Johnson<sup>22</sup> it was shown that insulin resistance could be produced in depancreatized dogs. Such work, then, would seem to discredit the above theory. They studied cases in which fever was produced following typhoid vaccine administration and also fever induced artificially by the cabinet method. It was found that certain cases showed some resistance following typhoid vaccine injections even without the presence of a systemic effect such as fever, and others exhibited no resistance despite a temperature elevation of four to six degrees. They conclude from these studies that fever itself most likely has very little to do with the production of insulin resistance. Possibly of minor importance is the depletion of carbohydrate reserves.

To some patients with well controlled diabetes, *histamine* in very mildly toxic doses was given with very little increase in the insulin requirement. As a result, the possibility arose that some such substance as this may play a rôle in the development of insulin resistance. Undoubtedly, this problem involves the functions of the liver, pituitary, adrenals, and certainly muscles, but, as yet, the mechanism is not known. Despite this, Greene and Keohen observe, as have others, that insulin resistance does not develop in all cases of diabetes during an acute infection. They point out that it may occur in the course of a given infection, and not subsequently in a comparable infection. It was their feeling that insulin resistance is more apt to be developed by patients whose diabetes is mild, rather than by the severe, labile diabetic. It would seem also that those patients developing insulin resistance with one infection

would have a recurrence of this resistance in subsequent toxemias.

Schreier<sup>23</sup> reports a case of insulin resistance studied at the New York Hospital in which the daily insulin dosage varied from 585 units to 1310 units on the day of death. Despite the increased dosage of insulin each day, the blood sugar levels showed a definite increase and on the thirteenth day the patient died in diabetic coma. Prior to death, she exhibited all of the classical signs of diabetic acidosis, namely, dryness of the skin due to dehydration, acetone on the breath, soft eyeballs, Kussmaul breathing in addition to the usual chemical abnormalities. It is of interest that Schreier noted definite allergic manifestations when the patient was first given insulin, and on examining the serum, insulin-neutralizing substances were present. Pathologically, fatty degeneration of the liver and hyaline degeneration of the islands of Langerhans were found.

This problem has been of extreme interest to the authors in view of a patient whom they have studied and followed for a period of several years at the Graduate Hospital of the University of Pennsylvania. This particular patient, a female now approaching 30 years of age, for the past four years has been taking between 300 and 400 units of insulin daily. Despite this large dosage, the writers were unable to keep her blood sugar level for the greater part of this period anywhere near normal limits, and interestingly enough, so far as known, she has never suffered a hypoglycemic reaction. They have attempted, while she was confined in the hospital, to produce a mild hypoglycemic reaction by giving her as much as 100 units of regular insulin in a fasting state, but with no evidence of hypoglycemia.

Every physician treating diabetes has experienced on innumerable occasions

the phenomena of well-controlled diabetics becoming markedly uncontrolled, and often going into acidosis as a result of infection, even though larger doses of insulin, thought to be sufficiently great, have been administered. Just recently, an elderly diabetic male under the authors' care, who for the past few years has been well controlled on diet alone, developed a pneumonia and required as much as 80 units of insulin daily to keep his blood sugar approximating the normal limits. After the pneumonia had cleared up the insulin dose was gradually decreased to the point that when he left the hospital he again was controlled on diet alone. This is a common occurrence and although the mechanism involved is not known, whether it be a decrease of endogenous insulin or due to some more complex mechanism, from a practical standpoint it is known to be imperative that one follow carefully with frequent blood sugar and urine examinations and give sufficient insulin to prevent the occurrence of acidosis. Infection has been, and still is, one of the most common predisposing factors in the onset of acidosis.

### Diabetic Infants

It has long been felt that the infants of diabetic mothers, in addition to a high mortality rate, are predisposed to hypoglycemia, asphyxia, congenital defects, and a tendency to gigantism. During the past year, Priscilla White<sup>24</sup> has reported a series of 125 consecutive pregnancies occurring in 119 different diabetic patients covering the period between January, 1936, and July, 1942. She included in this group only those successfully carried to the twenty-fourth week. She feels that the infant of a diabetic mother shows certain characteristics: First, a tendency toward gigantism, which in the series reported was due to obesity, edema, and

splanchnomegaly; second, hematopoiesis very much like that found in erythroblastosis; third, hyperplastic islet tissue, and, lastly, hypoglycemia which usually corrected itself. Following up her hormone studies previously done, she again emphasizes that coincident with an imbalance of the sex hormones of pregnancy is the abnormal obstetric maternal course and the high fetal mortality rate. This, she feels, suggests that the mechanism is a progestin-estrin-deficient metabolism and that the rise of chorionic gonadotropin and the showing of pregnandiol are practical tests which predict an abnormal clinical course for both the mother and the infant. When this was completed with the administration of sex hormonal preparations, the hormonal imbalance lowered the incidence of prematurity, toxemias, and more markedly decreased the fetal deaths.

This work of Dr. White is very interesting but as yet has not been confirmed by other workers, and a good many men who see large numbers of pregnant diabetics feel that the incidence of toxicity is no greater than in the nondiabetics and that they can be carried through the period of gestation without the use of hormone therapy.

### Obesity

The fundamental treatment of the obese patient is still dietary restriction. Obesity is the result of disproportion between the caloric intake and the expenditure of calories. According to Severinghaus,<sup>25</sup> excessive hunger may be due to hypoglycemia, habitual overfilling of the stomach, and certain dietary addictions. Decreased expenditure of calories may be associated with physical or economic handicaps, hyperthyroidism, and psychological situations, as there are certainly

constitutional and genetic types of obesity.

Colton, Segal *et al.*<sup>26</sup> have reported 300 cases treated by diet and appetite control. They found that the appetite was best controlled by *amphetamine* and *propadrine hydrochloride*. The diets given these patients were low in calories but were, for the most part, of bulky but low caloric foods. Other therapeutic agents used are *thyroid*, *ammonium chloride*, *xanthine* derivatives, and *belladonna*. The average weight loss for the entire group was two pounds per week.

The difficulty most often encountered in the treatment of the obese patient is the fact that he will not follow his diet closely. Reducing, in itself, is not difficult, provided one has the complete cooperation of the patient. Various therapeutic agents, as noted above, are used and some of them are undoubtedly helpful, but the most important factor is the adherence to the prescribed diet which may vary between 800 and 500 calories per day between patients.

The make-up of these diets in the authors' hands has been important and the high-Protein-low-Carbohydrate diet, first advocated by Dr. Frank Evans some years ago, is still the method of choice. As a rule, they make up a diet containing 1½ Gm. or more of Protein per kilo of ideal body weight, get 60 per cent of this amount as the Carbohydrate allowance. This, of necessity, should be made up of the 3 per cent and 6 per cent vegetables. No additional fat is added to the diet. It is well to bear in mind that there are probably 20 to 40 Gm. of fat inseparable from your protein portion. A diet, therefore, for a patient who should weigh 132 pounds would be 90 Gm. of Protein, 54 Gm. of Carbohydrate, and 20 to 40 Gm. of Fat.

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## RESPIRATORY SYSTEM

DANIEL B. PIERSON, JR., M.D.

## PNEUMONIA

## Pneumococcal Pneumonia

The need for standardization of diagnosis of pneumonia and accuracy of records and vital statistics is rather forcefully brought to attention by Faller, Quickel, and Smith<sup>1</sup> in their analysis of 377 deaths ascribed to pneumonia in various hospitals.

Using the classification of: (1) Primary Pneumonia; (2) Secondary Pneumonia; (3) Terminal Pneumonia, and (4) No Pneumonia, the contrast in their analysis and the hospital records is shown in the following table:

TABLE I

	Hospitals	Analysis
Primary Pneumonia...	261	177
Secondary Pneumonia.	69	61
Terminal Pneumonia..	47	66
No Pneumonia.....	0	73

They criticize the tendency of surgical services to attribute death to pneumonia rather than to surgery or primary surgical disease.

Prognostic significance of the gross character of sputum in pneumococcal pneumonia was analyzed by Frisch, Price, and Myers.<sup>2</sup> In 651 cases with rusty sputum the amount and character of sputum was correlated with standard prognostic criteria, outcome, and necropsy of fatal cases. Those having small amounts of viscid sputum had milder disease, fewer cocci in the sputum, lower mortality rate (6 per cent), and at necropsy the lungs were dry with relatively smaller areas of consolidation. The group having large amounts of sputum had more severe disease, more numerous cocci in the sputum, higher mortality rate (23 per cent), and at necropsy wet lungs with relatively large areas of consolidation. The pathologic physiology and

therapeutic significance awaits further study.

**Sulfonamides** still hold first place in pneumonia therapy. **Sulfamerazine** and **sulfapyrizine** are two of the newer drugs to receive comment in the past year. Flippin, Geffer, Domm, and Clark,<sup>3</sup> comparing 80 cases treated with sulfamerazine and 80 treated with sulfadiazine, determined that smaller doses of sulfamerazine, *viz.*, 3 Gm. (45 grains) intravenously as initial dose, then 1 Gm. (15 grains) every eight hours gave higher blood concentration of free drug than larger doses of **sulfadiazine**, *viz.*, 3 Gm. (45 grains) intravenously as initial dose, then 1 Gm. (15 grains) every six hours, the former giving a blood level of 10.9 mg. per cent, the latter 7.9 mg. per cent. Morbidity and mortality were slightly lower in the sulfamerazine group. However, in bacteremic cases the sulfamerazine group showed a mortality of 33.3 per cent, while the sulfadiazine group showed mortality of 18 per cent. Crystalurea was observed in 15 per cent of each group. Untoward reactions in both groups were meager.

**Sulfapyrizine**, as used by Ruegsegger, Brookins, Hamberger, and Grupen<sup>4</sup> in 105 cases (12 cases, etiology not found in blood or sputum), allowed mortality in only four cases, all of whom were over 50 years of age, had bacteremia, and evidence of other degenerative disease. An initial intravenous dose of 4 Gm. (60 grains) as 5 per cent solution followed by 1 Gm. (15 grains) every four hours by mouth gave signs of renal irritation. When the oral dose was changed to every six hours no renal irritation was noted. Toxic effects were rare.

**Sulfadiazine** has been highly effective in pneumonia therapy and its popularity is reflected in the literature.<sup>3, 5, 6, 7, 8</sup> Dowling, Hartman, Feldman, and Jenkins<sup>5</sup> compared the value of high and low

dosage of sulfadiazine in two similar pneumonia groups, finding the mortality rates approximately the same in both. Recovery was quicker in the larger dosage group as judged from morbidity, subsidence of fever, and time of resolution. The hospital stay in this group was 3.4 days shorter. They call attention to the effectiveness of the smaller dose in case of drug shortage, not improbable in wartime. Large dosage, 6 Gm. (90 grains) initially and 1 Gm. (15 grains) fourth hour; small dosage, 2 Gm. (30 grains) initially and  $\frac{1}{2}$  Gm. ( $7\frac{1}{2}$  grains) fourth hour.

Shackman and Bullowa<sup>6</sup> compared results of patients treated with **sulfadiazine** alone and those treated with **specific antipneumococcic serum** in addition. Of the 232 cases receiving chemotherapy alone a total mortality of 13.4 per cent was realized, though by excluding moribund cases dying within 24 hours of admission, the mortality is lowered to 8.3 per cent. The total mortality for the combined therapy group was 14.3 per cent in spite of the fact that the incidence of positive blood cultures was twice as great in this as in the chemotherapy group. The grave prognostic significance of type III pneumococcic infection, the presence of capsular carbohydrate in the blood, and the finding of positive blood cultures is again forcibly emphasized in both groups of their series.

While the use of antipneumococcic serum has decreased in proportion to the increase in effective chemotherapy, its importance has again, within the year, been stressed by most authors, *viz.*, Faller *et al.*,<sup>1</sup> Flippin *et al.*,<sup>3</sup> Ruegsegger *et al.*,<sup>4</sup> Dowling *et al.*,<sup>5</sup> Schackman and Bullowa,<sup>6</sup> Bortz,<sup>7</sup> Kent,<sup>8</sup> and others. The decision for or against serotherapy hinges on the physician's clinical evaluation of the individual case, but the pres-

ence of a virulent type pneumococcus with positive blood culture and/or capsular carbohydrate in the blood strongly suggests its use in combination with chemotherapy or alone if for any reason chemotherapy is impracticable.

Barach<sup>9</sup> reports successful management of sulfa-resistant pneumonias by the use of *oxygen-helium mixtures* or 100

the bronchial tree tends to retard venous blood flow and its only contraindication is shock, in which venous return to the heart is already inadequate. The usefulness of this principle is evident in bronchopneumonia, atypical pneumonias, cardiac failure, and pulmonary edema from any cause. The positive pressure may be obtained by immersing the end of the

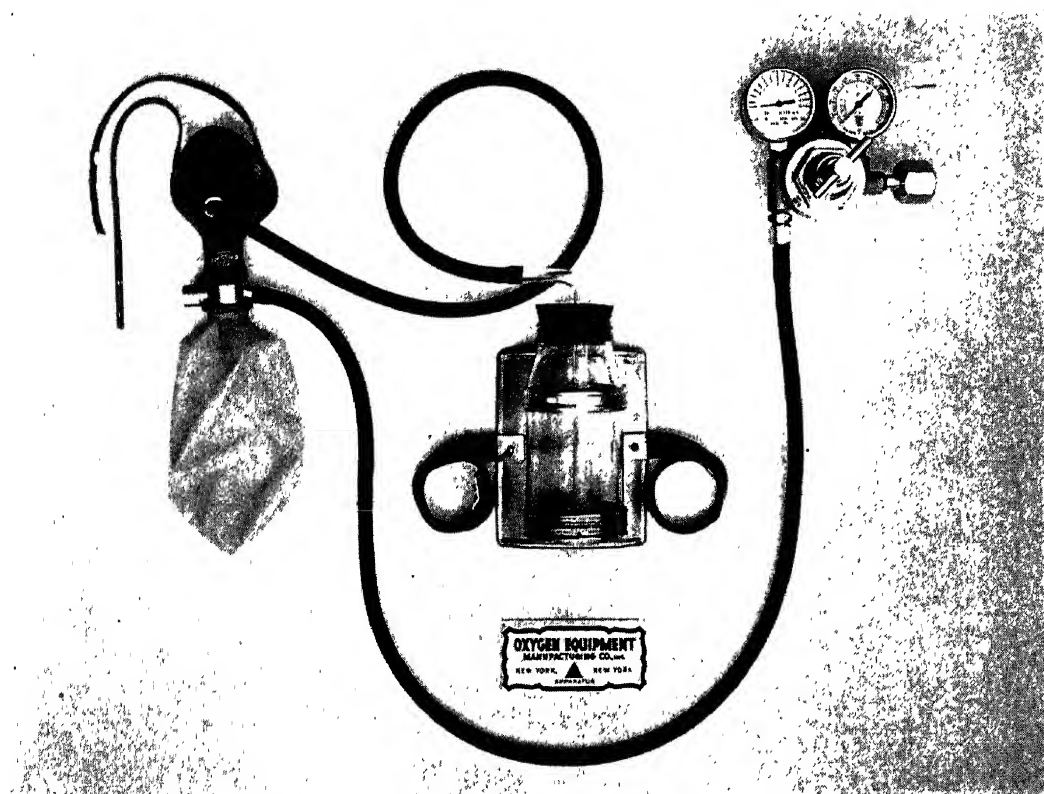


Fig. 1—Oxygen meter mask with attachment to water bottle to provide pressure during expiration. (A. L. Barach: Ann. Int. Med.)

*per cent oxygen* administered under positive pressure of 1 to 6 cm. of water. *Neosynephrine* 1 per cent for vasoconstriction and 1 to 100 *epinephrine* for bronchial dilatation are introduced by passage of the O<sub>2</sub> mixture, 5 liters per minute, through a nebulizer containing the liquids. The positive pressure encourages dilatation of the passages, reduces tendency to pulmonary edema or exudates by pressure on the capillaries and cells, and increases O<sub>2</sub> absorption by the capillaries. Positive pressure in

expiratory tube from hood or mask to the desired cm. depth below water as shown in Fig. 1. A more practicable apparatus is Barach's<sup>10</sup> modification of an injector mask previously described by him. The expiratory valve is replaced by a disc with varying sized openings graduated to produce 0 to 4 cm. water pressure in exhalation. An emergency valve automatically functioning when the collecting bag collapses prevents distress to the patient in case the administered gas is exhausted.



Prophylaxis of pneumonia is again suggested by Bortz<sup>7</sup> by the use of *sulfonamides* early in respiratory infection, also by Faller *et al.*<sup>1</sup> where conditions may predispose the patient to susceptibility to pneumonia. Robertson<sup>11</sup> questions the efficacy of this prophylactic procedure because of his concepts of the inception of pneumonia on a stasis basis.

literature, ranging from the official military primary atypical pneumonia, etiology unknown,<sup>23</sup> through pneumonitis, virus pneumonia, and viral pneumonia<sup>13</sup> to acute bronchiolitis with associated atelectasis.<sup>14</sup>

The ideal circumstances for studying large series of cases offered by military groups probably accounts for the official

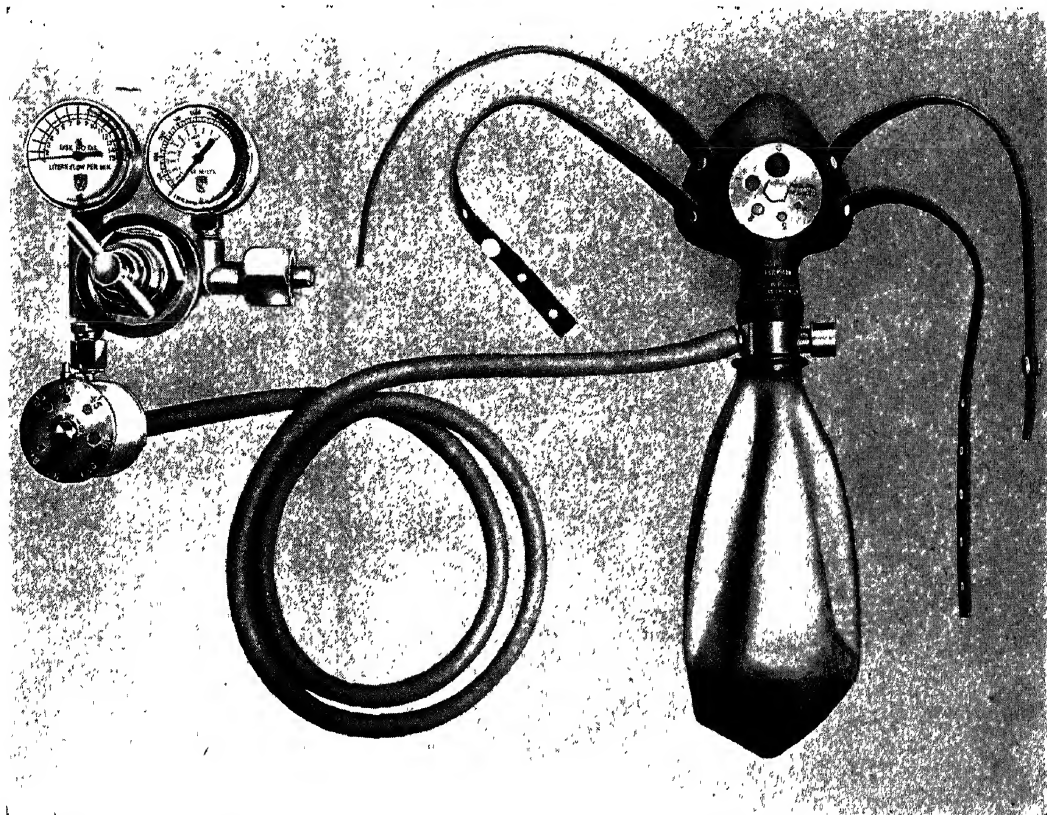


Fig. 2—An oxygen mask metered for positive pressure, showing air mixer, collecting bag, emergency intake valve, adjuster for control of expiratory pressure, and expiratory flutter valve. (A. L. Barach: *Ant. Int. Med.*)

Rusk and van Ravenswaay<sup>12</sup> found no essential difference in recovery time, hospital stay, or incidence of pneumonia in a carefully controlled group of 670 cases of simple respiratory tract infection, half treated with adequate doses of sulfadiazine and half treated symptomatically.

### Primary Atypical or Viral Pneumonia

Confusion of terminology of this clinical entity still reigns throughout the

military terminology dominating the year's literature. Most authors agree that the etiologic organism in this disease is a filterable virus and Reimann<sup>13</sup> suggests the adjective "viral" to describe the pneumonia, as grammatic and more specific, as many bacterial agents can be responsible for atypical pneumonia. Campbell, Strong, Grier and Lutz,<sup>14</sup> from the pulmonary pathology point out the absence of true pneumonia and the presence of bronchiolitis and associated



atelectasis and suggest this pathology nomenclature as an accurate name for the disease.

That the disease has been prevalent this year is evident by the many reports on various aspects of it from widely divergent localities. Early in the year Reimann<sup>13</sup> advanced in order of probability three reasons for the relative and actual increase in its incidence in recent years as follows:

"(1) Their actual increase may be a manifestation of the natural fluctuation in incidence common to many infectious diseases.

"(2) Diagnosis is made more frequently because of interest in the disease and because of the freer use of roentgenography, and

"(3) A diminution in the incidence of pneumococcal pneumonia induced naturally and also artificially with chemotherapy emphasizes a relative increase of unusual forms to which little attention has been paid in the past." The widespread epidemic proportions to which the infection has climbed in the latter part of the year cast the bulk of evidence for the validity of reason No. 1.

Evidence as to the etiology of this pneumonia is both direct and deductive and all in favor of a filtrable virus. The known viral diseases, when complicated by pneumonia (exclusive of secondary invaders), show the same type of pulmonary pathology and clinical course as does the disease under discussion.<sup>15</sup> Also in the atypical pneumonias submitted to thorough study with animal inoculation, cross immunization and neutralization, a virus has been the offender. The question has arrived as to whether the apparently related viruses might be descendants of a single parent modified by adaptation to different hosts, whether they may be interchangeable, whether each represents a specific type analogous

to the pneumococcic types, or whether they are identical.

The general forms of the syndrome as classified by Reimann<sup>13</sup> we think most worthy of note:

"(a) As a sporadic, nonseasonal, slightly contagious, systemic disease with a relatively long incubation period of ten days to two weeks, occurring in isolated instances or in small groups of cases of varying severity, centering around a single source of infection. . . . The disease appears to be a systemic one, often with splenomegaly and nervous symptoms, in which the lungs are incidentally affected. Manifestations of pulmonary involvement may be delayed for days. . . . The upper part of the respiratory tract is seldom affected to the extent that it is in the other group. In the individual case, however, certain clinical signs and symptoms, such as the normal or subnormal leukocyte count, the roentgenographic appearance of the lungs, sweating, unproductive paroxysmal cough, bradycardia, photophobia, and the duration, are the same as in the next group.

"(b) As the severest cases in large epidemics of mild, highly contagious, local disease of the respiratory tract, commonly called colds, grippe or influenza, occurring usually in the cold months. The incubation period appears to be short, a matter of one to several days. Generally, the disease is indistinguishable from influenza B, yet it is caused by a different agent or agents, and the three or more specific diseases often occur together in varying proportions in the same epidemic. It seems to be primarily a mild infection of the upper part of the respiratory tract which, in the occasional case, already affects the lungs or spreads downward to cause pneumonia and severe disease." This concept is borne out by several reported series.<sup>12, 24, 26</sup>

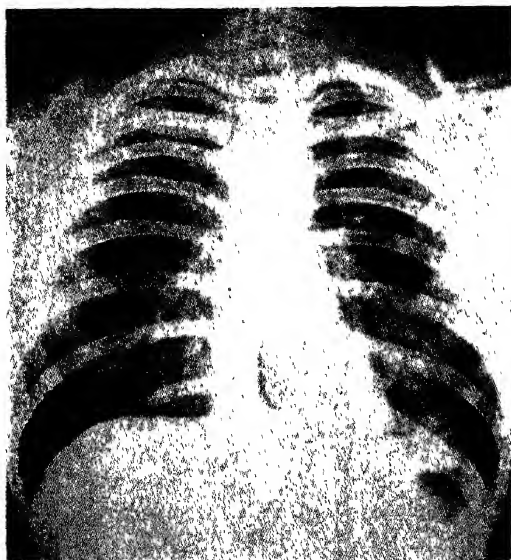


Fig. 3—"Cotton-wool" appearance of centrally located early infiltration and partial consolidation. (A. E. Seeds and M. L. Mazer : Am. J. Roentgenol.)

The paucity of clinical signs early in the disease and the necessarily tedious task of proving the viral etiology throws the burden of proof of diagnosis on clinical deduction and to no small extent on roentgenographic interpretation. Of the several writings commenting on the roentgenographic findings appearing recently, the writer considers two particu-

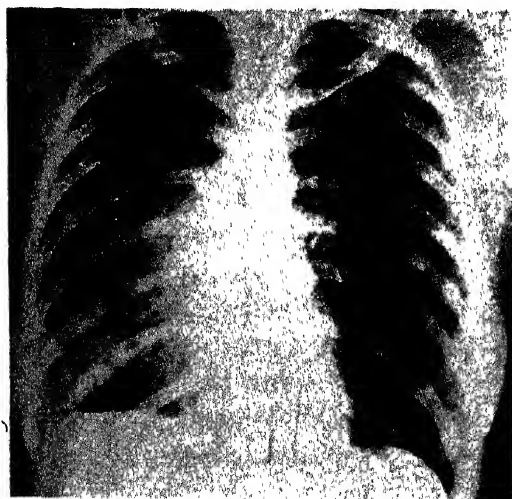


Fig. 4—"Cotton-wool" appearance in so-called inverse phase or resolution with new area or unit developing from right upper hilum. (A. E. Seeds and M. L. Mazer : Am. J. Roentgenol.)

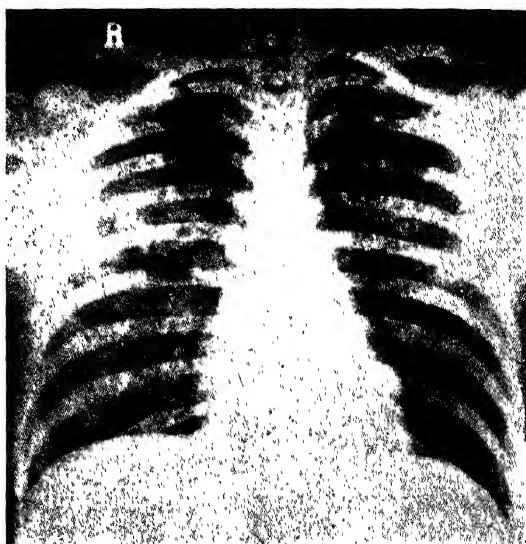


Fig. 5—Early "wire-grass" type infiltration characterizing midresolution. (A. E. Seeds and M. L. Mazer : Am. J. Roentgenol.)

larly worthy of special note, *viz.*, Seeds and Mazer,<sup>16</sup> and Campbell, Strong, Grier, and Lutz.<sup>14</sup> The former authors from study of 221 cases propound constant features of roentgenologic pattern of atypical or viral pneumonia which are of value in differential diagnosis. Their idea of the process from structural analysis is presented in the following outline and illustrations of it with also some contrasting lesions for standardization are furnished.

1. An infiltrative process at the onset :

- (a) First progressively peribronchial from the hilum and then irregularly interbronchial; earlier in the more proximal portion.

- (b) Customarily clearly definable as to limits in spite of its disregard for segmental or lobar structural limits, usually involving more than one segment and frequently parts of more than one lobe.

2. Quickly accompanied by a cotton-wool appearance of partial or semiconsolidation :

- (a) This is scattered through the area of infiltration; usually distributed in a radial progression also.

- (b) Frequently subsequently (six to 24 hours) coalescing.

- (c) Occasionally eventually (24 to 48 hours) filling approximately a whole lobe to simulate lobar pneumonia but, so far as we have seen,

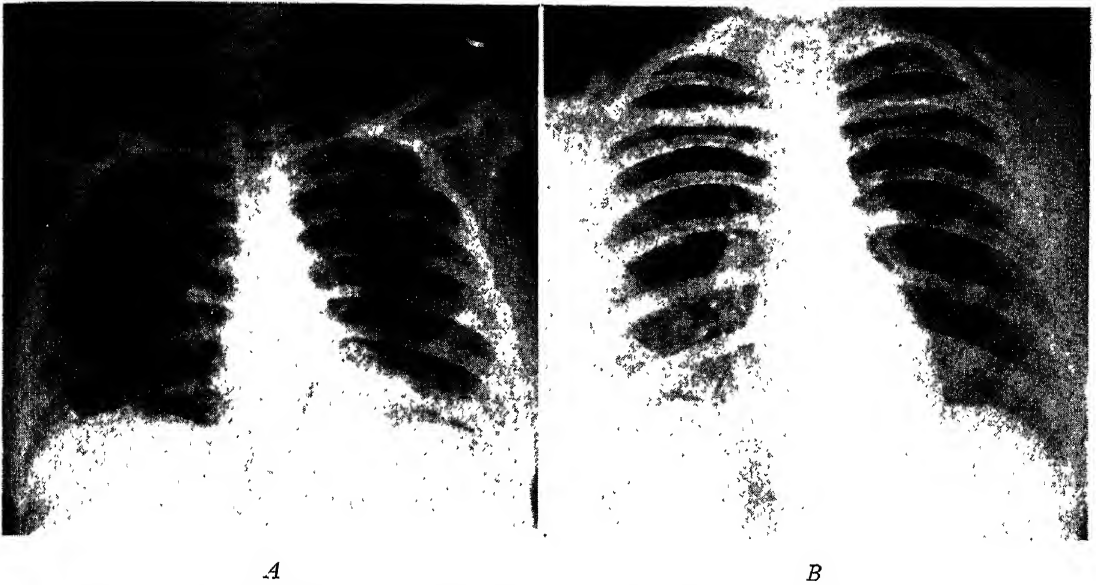


Fig. 6—*A*, Late "wire-grass" type infiltration (pseudofibrosis). *B*, Same case showing the lungs entirely clear in one week. (A. E. Seeds and M. L. Mazer: Am. J. Roentgenol.)

always managing to present a striated infiltrative-type background rather than a pure homogeneity.

(*d*) Usually establishing a fixed distribution for any one area in two to three days, which afterward behaves as a "unit."

3. Resolution or absorption begins:

(*a*) By generalized and uniform progressive (three to five days) loss of density throughout the "unit."

(*b*) The development of the appearance of "wire-grass" infiltration or "pseudofibrosis" (suggesting a relatively simple inverse of the developing process).

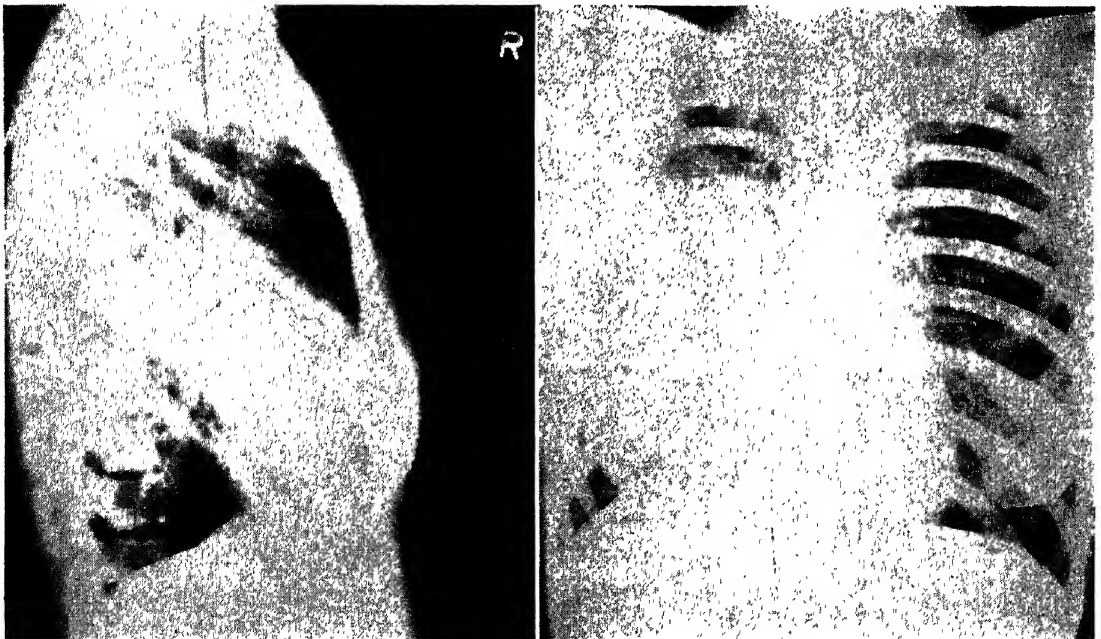


Fig. 7—Extensive distribution simulating lobar pneumonia. Actually the extension is beyond lobar lines and a striated characteristic is retained. (A. E. Seeds and M. L. Mazer: Am. J. Roentgenol.)

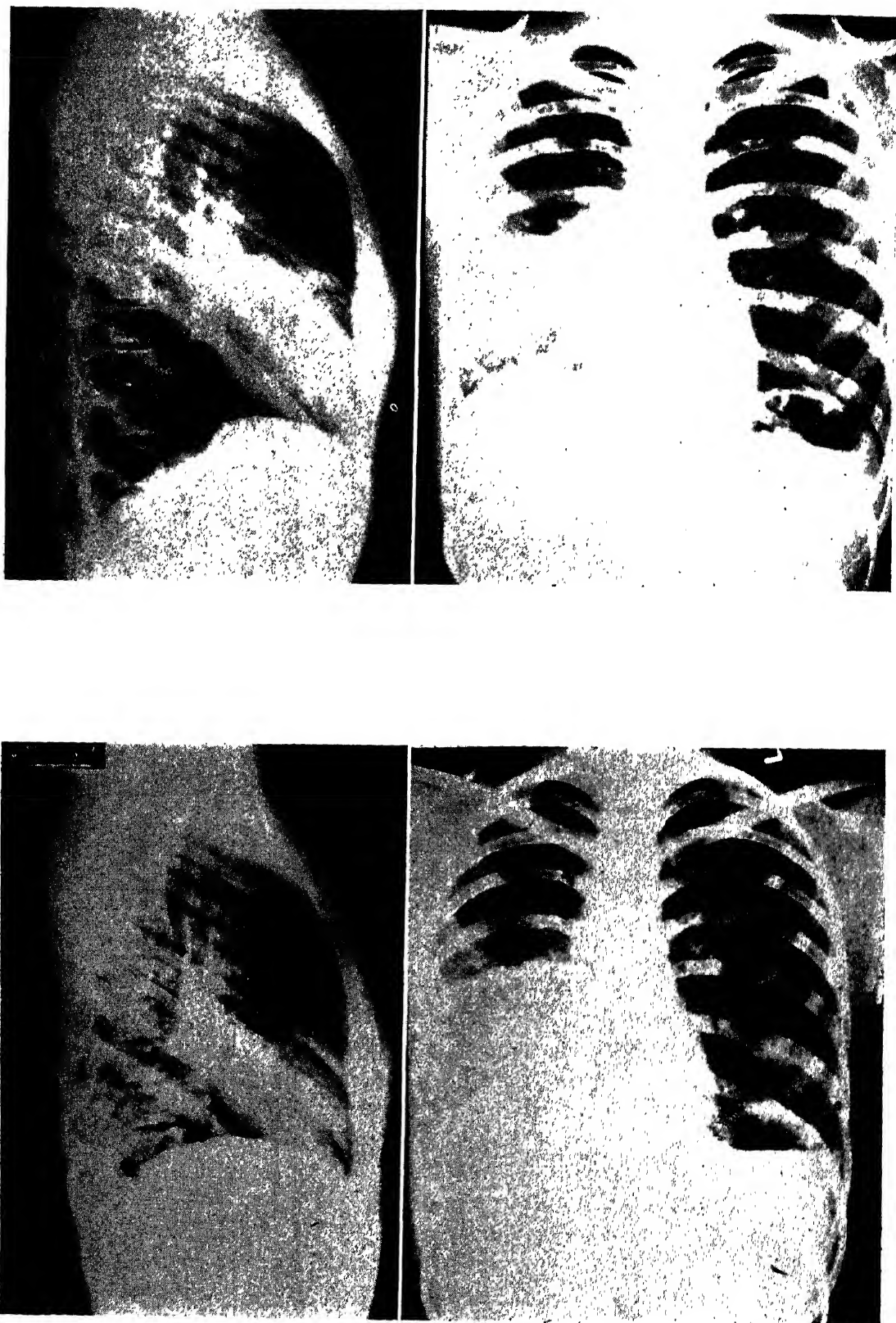


Fig. 8—Two examinations of same patient within 48 hours, showing (top to bottom) distribution simulating lobar pneumonia, but developing lesion characteristics rapidly, indicating a non-pneumococcus process. (A. E. Seeds and M. L. Mazer: *Am. J. Roentgenol.*)



Fig. 9—Typical process and 72-hour sequence in 7-year-old child. (A. E. Seeds and M. L. Mazer: *Am. J. Roentgenol.*)

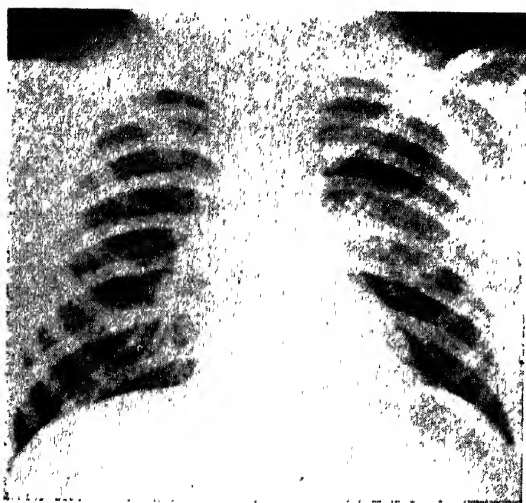


Fig. 10—Typical location, uniform density, and definition of lobular pneumococcus pneumonia in a child. (A. E. Seeds and M. L. Mazer: *Am. J. Roentgenol.*)

(c) Eventual progressive complete clearing of this process in five to 14 days, usually five to eight days in cases of single "units."

4. Occasional development of multiple "units" with:

(a) Subsequent definite dates of onset and individual chronology.

(b) Rarely involving all visible parts of the lung.

(c) Usually no one unit disturbing the approximate prearranged chronology of any forestated unit.

5. Occurring quite typically in children.

The authors recorded only one typical case under six months, but many both under and over two years. They admit the probable variant of the process in time cycles of the disease and in different localities.

Campbell, Strong, Grier, and Lutz,<sup>14</sup> from a thorough analysis of 200 cases of atypical pneumonia with pathologic studies, in one fatality deduct that the process is primarily an inflammatory process in and around the bronchi and bronchioles and that atelectasis follows the plugging of the tubular structures. They contend that a true pneumonic process does not exist and correlate the clinical and roentgenographic picture with the pathologic findings. Table II and Figures 13 through 20 are self-explanatory.





Fig. 11—Typical middle stage (5 days after onset) process with typical distribution differing from lobular pneumonia in similar location having similar distribution but different appearance. (A. E. Seeds and M. L. Mazer: *Am. J. Roentgenol.*)

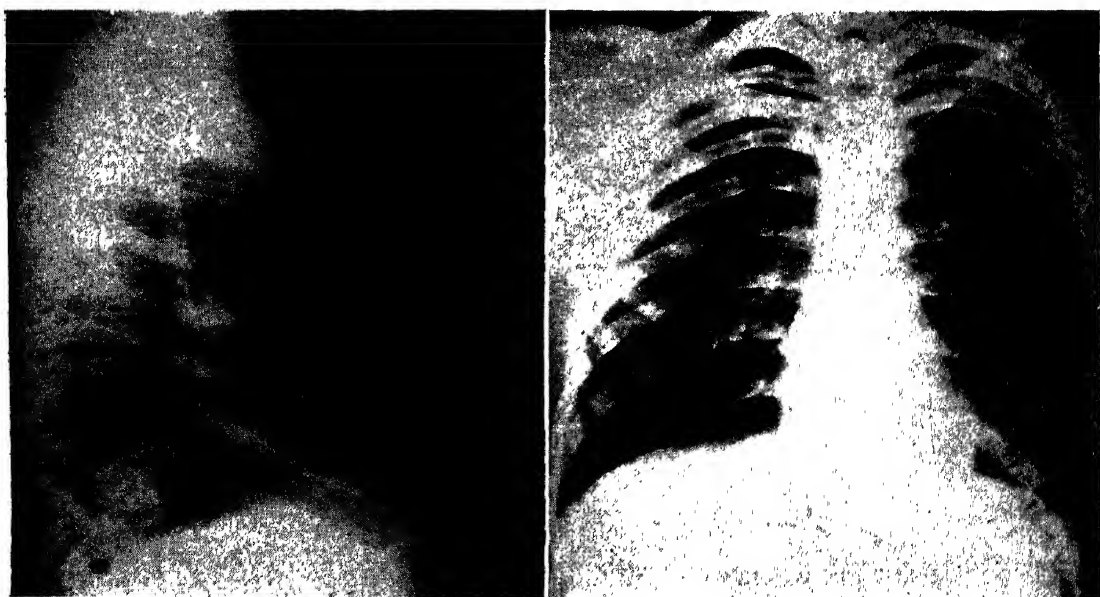


Fig. 12—Characteristic localized segmental or lobular pneumococcus pneumonia of location and size similar to Fig. 11. (A. E. Seeds and M. L. Mazer: *Am. J. Roentgenol.*)

TABLE II\*  
STATISTICAL SUMMARY OF RADIOGRAPHIC  
FINDINGS

Condition	Cases	Per Cent
1. Basilar involvement.....	162	81
2. Bilateral involvement.....	44	22
3. Right sided involvement...	78	39
4. Left sided involvement....	78	39
5. Upper lobe involvement only	23	11
6. Right upper lobe involve- ment only.....	22	10.5
7. Left upper lobe involvement only.....	1	0.5
8. Involvement of the left upper and lower lobes only.....	10	5
9. Involvement of the right upper and lower lobes only.....	4	2
10. Involvement of all lobes....	1	0.5
11. Involvement of both lower lobes and right upper....	4	2
12. Involvement of upper lobe irrespective of other lobe.	36	18
13. Involvement of right lower and left upper lobe.....	3	1.5
14. Presence of pleural fluid (very slight in every in- stance).....	12	6
15. Elevation of diaphragm or shift of mediastinum or both.....	38	19
16. Spread of lung disease after initial film study.....	12	6
17. Average number of days for film clearing.....	11.5	days
18. Case negative on admission and developed densities later.....	1	0.5

\* T. A. Campbell, P. S. Strong, G. S. Grier, 3d,  
and R. J. Lutz: J. A. M. A.

Gedgoud,<sup>17</sup> reporting on "Virus Pneumonitis" in infancy, reiterates the plugging of bronchioles, marked peribronchiolitis, and cytoplasmic inclusion bodies common to the bronchiole epithelium in various types of viral pneumonias. Similar inclusion bodies were found in the pharyngeal and vaginal smears of 25 of 35 women, apparently without upper



Fig. 13—(Case 1.) Basilar stringy and mottled density seen in 81 per cent of our cases. The radiating stringy densities represent diseased bronchi and bronchioles. The hazy mottled density represents atelectatic lung. Note the platelike areas of atelectasis with associated elevation of the right leaf of the diaphragm. (T. A. Campbell, P. S. Strong, G. S. Grier, 3d, and R. J. Lutz: J. A. M. A.)

respiratory infection, thus discrediting them with diagnostic significance in the syndrome.

Therapy of atypical pneumonias has in the past been conspicuously lacking in any degree of specificity as we might anticipate in a disease whose etiology is not specifically known. The virus or viruses are not vulnerable to *sulfonamides*, hence their use could be expected

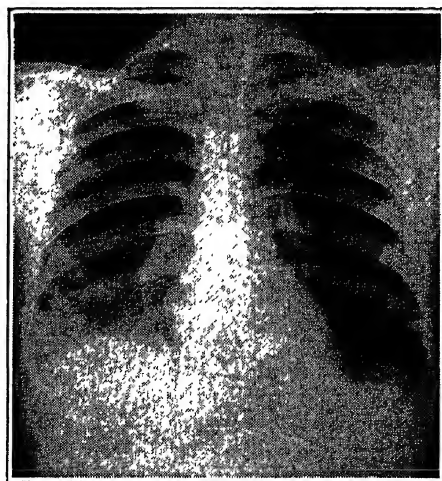


Fig. 14—Patchy atelectasis of the right upper lobe, resembling pulmonary tuberculosis. (T. A. Campbell, P. S. Strong, G. S. Grier, 3d, and R. J. Lutz: J. A. M. A.)



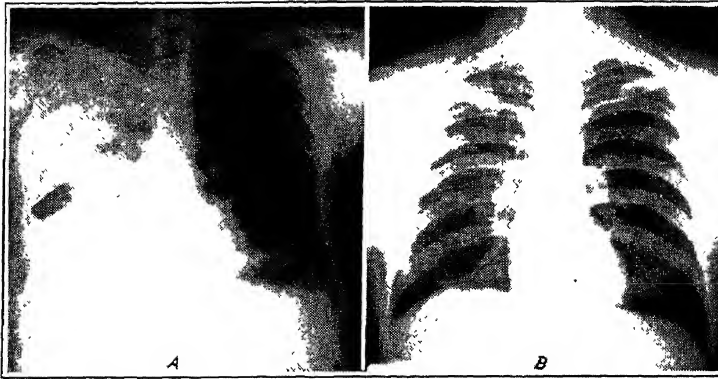


Fig. 15—*A*, The homogeneous density in the right upper lobe has the appearance of a lobar pneumonia. However, the decided right-sided shift of the trachea and heart with elevation of the diaphragm reveals its true atelectatic nature. *B*, Same, 17 days later, demonstrates complete re-aeration of the right lung. The mediastinal structures and the right leaf of the diaphragm have assumed their normal positions. (T. A. Campbell, P. S. Strong, G. S. Grier, 3d, and R. J. Lutz: J. A. M. A.)



Fig. 16—Complete collapse of the right upper lobe is noted with platelike areas of atelectasis overlying each leaf of the diaphragm. The mediastinal structures have been pulled to the right side. (T. A. Campbell, P. S. Strong, G. S. Grier, 3d, and R. J. Lutz: J. A. M. A.)

to benefit only where secondary infection prevails. Some of the series in which sulfonamides were used show slightly longer recovery time than comparable groups treated symptomatically with *antipyretics*. *Convalescent sera* are of doubtful efficacy at most and have been largely abandoned even in more specific viral infection, as psittacosis.<sup>13</sup>

Two papers show enthusiasm for *roentgenotherapy* in primary atypical pneumonia. Correll and Cowan<sup>18</sup> observe that one or usually two irradiations of 112 r each on consecutive days in

acute cases (within four days of admission) reduced the febrile period, total number of sick days, and the days for resolution roughly 50 per cent in 22 of 23 cases treated. One showed no benefit to roentgenotherapy. As controls, they used the remainder of 155 cases treated symptomatically and with sulfa drugs.

In nine patients failing to resolve in 30 days on routine treatment, seven (or 77.7 per cent) cleared to x-ray within an average of four days after one or two roentgen treatments; 22.3 per cent of the chronic cases failed to benefit.

Oppenheimer,<sup>19</sup> using smaller dosage of *roentgenotherapy*, viz., 35 to 45 r for children and 50 to 60 r for adults in acute stages, and 50 to 70 r and 70 to 90 r respectively when infection had obtained a week or longer, observed generally a gradual return of temperature to normal within 16 hours after one treatment. Considerable diminution of both cough and general distress paralleled the fever drop. Increase in sputum expectoration obtained about 24 hours after treatment and the patients usually were well enough for discharge from the hospital in another day or two. The persistent cough which usually accompanies convalescence of untreated pa-

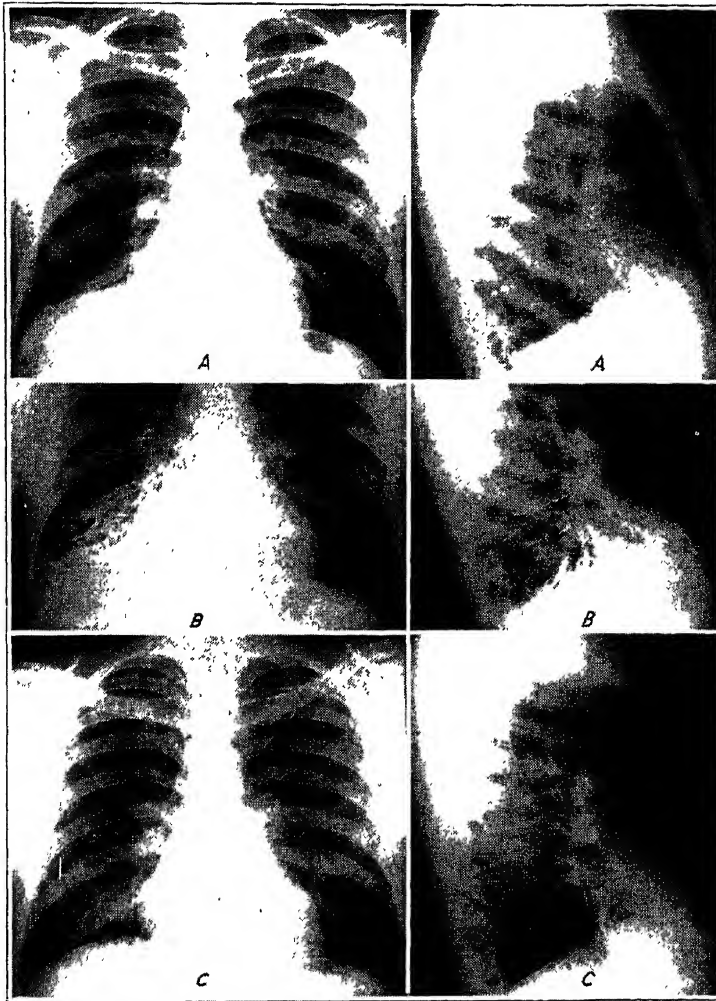


Fig. 17—*A*, Initial film study done on July 5, 1942, demonstrates a dense horizontal band of atelectasis overlying the right leaf of the diaphragm. *B*, Studies made with iodized oil on August 30, after the right lower lung field failed to re-aerate, demonstrates the crowded lower and middle lobe bronchi typical of atelectasis. Note the bronchiectasis. *C*, Reaeration is shown on a progress study done on September 11. Note the iodized oil remaining in one of the bronchiectatic bronchi of the right lower lobe. (T. A. Campbell, P. S. Strong, G. S. Grier, 3d, and R. J. Lutz: *J. A. M. A.*)

tients failed to develop in the early treated group. In cases treated after a week of infection, the temperature usually dropped to slightly above normal, but paroxysmal cough persisted and there was frequently a temperature rise after three to four days, necessitating a second or even a third irradiation. In two patients treated 16 and 23 days after onset, several irradiations with increasing doses up to 300 r failed to effect therapeutic results.

Mortality rates have been low generally in reported series, particularly in adults, and the fatalities have been in

so-called complicated cases, such as encephalitis,<sup>20</sup> which one might expect more frequently in severe forms of viral disease. Encephalitis, myelitis, and meningitis were present in one.<sup>14</sup> Atypical pneumonia accompanied by recurrent pericarditis was reported in one case.<sup>21</sup> Recovery obtained with pleuropericardial and diaphragmatic adhesions as only discernible residue.

Similarity to apical tuberculosis in atypical pneumonias of the upper lobes frequently requires serial films for differential diagnosis.<sup>14, 25</sup>

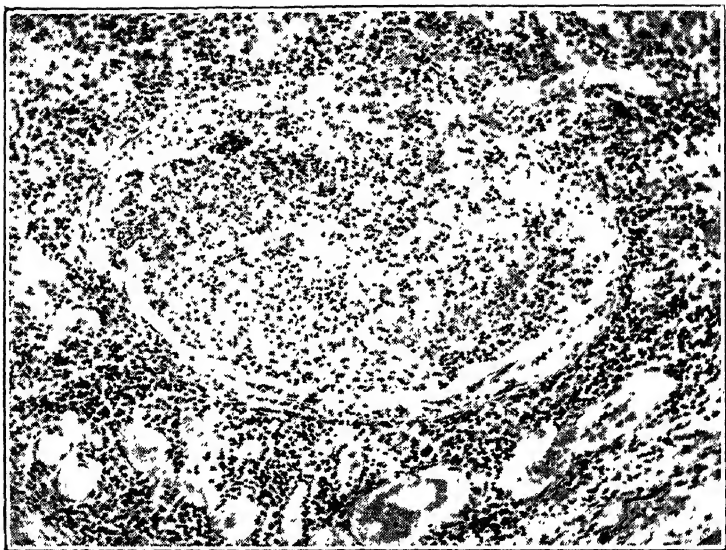


Fig. 18—Severe bronchitis with peribronchial infiltration. Note the intrabronchial cellular exudate. (T. A. Campbell, P. S. Strong, G. S. Grier, 3d, and R. J. Lutz: J. A. M. A.)

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Interest in this malady, as usual, has centered around the relief of the acute attack. The search for new effective drugs or combinations of drugs has continued, but to date nothing has been as effective as *epinephrine*, either by hypodermic injection or by inhalation of vapor from a nebulizer.

Dryness and irritation of the upper respiratory tract are the outstanding disagreeable side effects of inhalation of

nebulized 1:100 epinephrine. Lockey,<sup>27</sup> by employing a 5 per cent glycerinized solution, of 1:100 epinephrine, found these unpleasant reactions were reduced 82 per cent. His formula and method of preparation are as follows:

Suprarenal crystals .....	10 Gm.
Sodium chloride .....	9 Gm.
Chlorbutanol .....	5 Gm.
Sodium bisulfite .....	0.9 Gm.
Dilute HCl (10% U. S. P.)...	20 cc.
Glycerin .....	50 cc.
Distilled water to make.....	1000 cc.

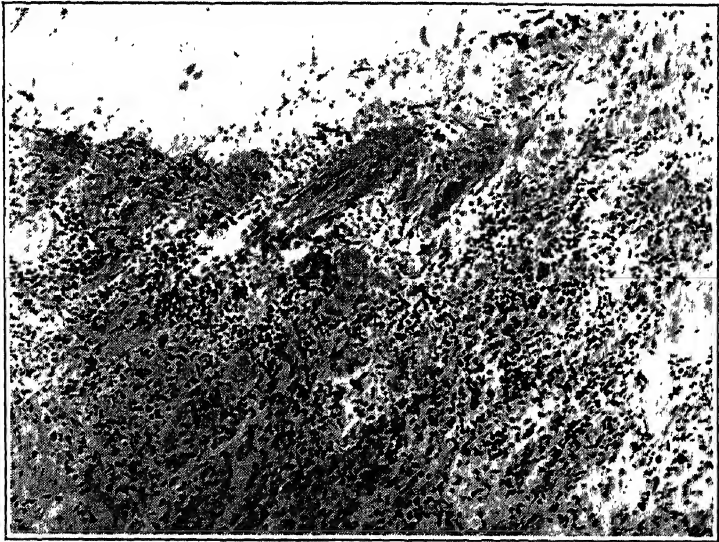


Fig. 19—Alveolar collapse with interstitial round cell infiltration. (T. A. Campbell, P. S. Strong, G. S. Grier, 3d, and R. J. Lutz: J. A. M. A.)

"Eight hundred fifty cc. of triple distilled water and 50 cc. of glycerin are heated to boiling to remove the dissolved air. The heat is shut off and the chlorbutanol and sodium chloride are added. The solution is cooled to room temperature and the sodium bisulfite is added.

"Ten Gm. of suprarenal crystals are dissolved in 20 cc. of 10 per cent HCl and added immediately to the above solution.

"The pH is then adjusted to 3.0 (a fluctuation from 2.9 to 3.1 is permissible). If necessary, a few drops of dilute sodium hydroxide solution may be used to bring the pH to 3.0. In case the HCl is a little weak, a small amount of normal HCl should be added.

*Ascorbic acid*, in 0.1 to 1 Gm. ( $1\frac{1}{2}$  to 15 gr) dosage, intramuscularly, is favored by Moreno for use in acute attacks.<sup>29</sup>

*Aminophyllin*, in 0.4 to 1 Gm. (6 to 15 gr) dosages, is still in good repute, either alone or in variously combined therapy.<sup>30</sup>

*Oxygen inhalation* naturally holds its physiologic therapeutic place; in combination with *helium*, it has shown some encouraging effects in the hands of Barach,<sup>30</sup> whose rather vigorous and

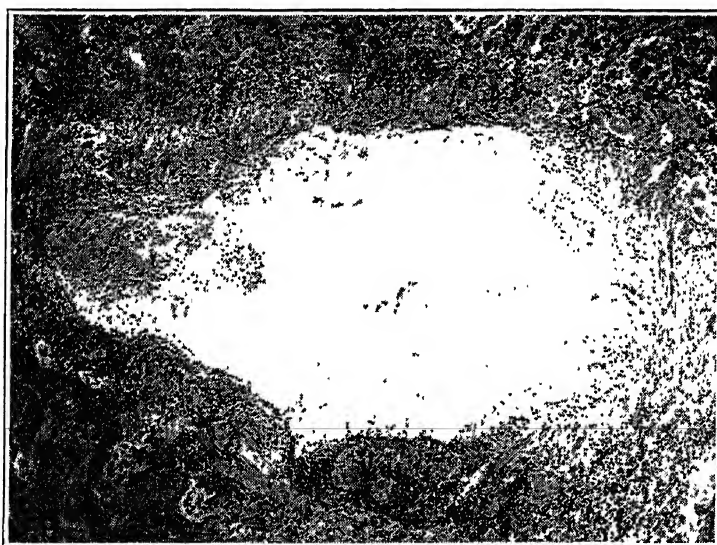


Fig. 20—Extensive interstitial round cell infiltration and well-defined atelectasis as seen under low power. (T. A. Campbell, P. S. Strong, G. S. Grier, 3d, and R. J. Lutz: J. A. M. A.)

"Distilled water is added until the volume is exactly 1000 cc. The solution is then filtered and filled into bottles (avoid the use of metal apparatus in the preparation of the material)."

This preparation is as stable as to color and effectiveness as other 1:100 solutions and may be used either in the hand nebulizer by the patient or by continuous oxygen spray.

*Nicotinic acid* in 50 mg. doses intravenously once or twice daily, has shown favorable results for Melton<sup>28</sup> in relieving acute attacks. In 50 mg. to 100 mg. doses orally, two or three times daily, frequency and severity of attack have been reduced in chronic cases.

somewhat all-embracing routine of therapy and the results are considered worthy of outline here. Hospital cases admitted in status asthmaticus were given rectally 0.5 to 0.6 Gm. ( $7\frac{1}{2}$  to 9 gr.) of *aminophyllin* in 20 cc. of water. Then inhalation of a spray of 0.5 cc. of 1:100 *epinephrine* vaporized by a stream of five liters of oxygen per minute through a nebulizer was administered. In some instances, this was followed by a spray of 1 cc. of 1 per cent *neosynephrine*. In excitable or nervous patients, 1 or 2 mg. of *dilaudid* was injected, or in some 2 mg. of dilaudid were incorporated in the

rectal aminophyllin. The patient was then placed in the *helium-oxygen hood* for two hours with 25 to 35 per cent oxygen (pending the absence or presence respectively of emphysema) and the rest helium. The *epinephrine spray*



Fig. 21—Low power photomicrograph of bronchiolar epithelium in a fatal case of asthma of 6 years' duration. Practically all of the cells are nonciliated secreting cells instead of the ciliated cells normally found in this epithelium. A few ciliated cells are found deep in the folds. The folding indicates constriction of the bronchiole. (A. C. Hilding: *Ann. Otol., Rhin. and Laryng.*)

was repeated in the afternoon and the patient again placed in the helium-oxygen hood for two hours. The nebulizer was used more frequently if needed. In a few very severe cases the hood was used again for two hours in the evening. A positive pressure of 3 to 4 cm. water was maintained within the hood except in cases with inspiratory dyspnea, when it was raised to 5 to 6 cm. In the evening the aminophyllin instillation was repeated and dilaudid included if needed.

**Aminophyllin instillations and oxygen-helium inhalations** were continued twice daily for five days; then stopped in most instances. Rectal aminophyllin was continued at home for one to five weeks in a number of patients. One cc. of *saturated potassium iodide* was given thrice daily during hospitalization; twice daily for two to three weeks after discharge, then once daily.

Ambulatory therapy included *aminophyllin instillation* with instructions for self-administration at bedtime, 1:100 *epinephrine* spray followed by *helium-oxygen inhalation* by a meter injector mask<sup>10</sup> at 7 to 9 liters per minute from a 20 per cent oxygen-80 per cent helium tank with 1 to 4 liters of oxygen added by a Y tube if needed, as in emphysema or to maintain the oxygen concentration between 22 and 25 per cent. *Potassium iodide* was given as in former schedule.

Aminophyllin may have to be reduced if nausea prevails but rarely below 0.4 Gm. (6 gr.). If rash develops, the iodides are temporarily suspended.

Results in 46 therapy courses in 26 hospital patients were disappearance or very mild residual asthma in 34 instances, restoration of epinephrine sensitivity and moderate asthma in nine instances, and little or no improvement in three instances.

In 54 courses of ambulatory therapy, there was disappearance of asthma or very mild asthma in 23, a restoration of

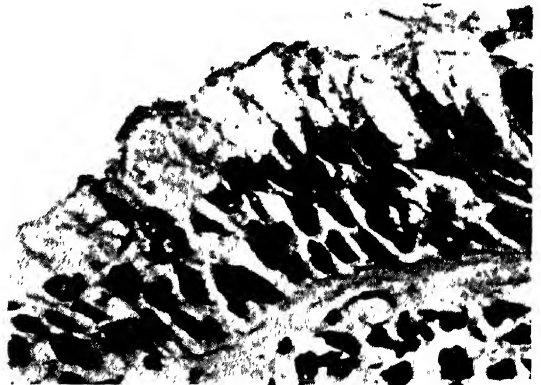


Fig. 22—High magnification of a field from Fig. 21. (A. C. Hilding: *Ann. Otol., Rhin. and Laryng.*)

epinephrine sensitivity with moderate persistence in 17, and little or no improvement in 14 instances.

Of 91 hospital and ambulatory courses of therapy, improvement persisted less than four weeks in 36 instances, one to

four months in 20 instances, five to 12 months in 20 instances and for one year or more in 15 instances.

Of 40 courses of rectal aminophyllin therapy alone in 20 patients, disappearance or very mild asthma obtained in eight instances, restoration of epinephrine sensitivity and moderate asthma in 14 instances, and little or no improvement in 18 instances. The duration of improvement in 15 of these patients receiving 25 courses of rectal aminophyllin was, in 12, one to four weeks; in 11, one to four months; and in two, six to 12 months.

*Roentgen therapy* in asthma has been discussed by Hull, Balyeat, and Chont,<sup>31</sup> who advocate a cross-fire tech-

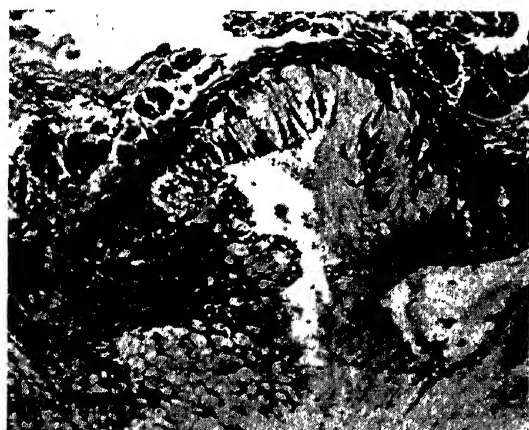


Fig. 23—The group of epithelial cells in the right center have become mucin-producing cells. Note how the mucus strand which has been secreted has fused with the mass in the lumen, but remains attached deep within the cells which produced it. Some of the nuclei look as though they had been dragged out of position by traction. There are still some ciliated cells remaining on both sides of the mucus strand. (A. C. Hilding: *Ann. Otol., Rhin. and Laryng.*)

nic irradiating large areas of the lung fields rather than the customary concentration on the hilar areas. The thorax is divided into six irradiation fields, right and left, lateral. Right and left oblique front and back. Two fields are irradiated at a sitting with 100 r of fil-

tered radiation each. The total course administering 800 r to 1600 r, pending the severity of the case; 50 per cent of their 1500 cases received one course in the year; 35 per cent received two courses,



Fig. 24—Low power photomicrograph of bronchial epithelium in a fatal case of asthma of 20 years' duration. The entire epithelium is melting into the secretion accumulated in the lumen. There are no ciliated cells whatever in this area. It can readily be understood from this illustration why the mucinous mass contained in the air passages remains in place. There are no cilia to move it. One can also see why it clings to the wall so tenaciously when attempts are made to remove it by aspiration or by means of forceps. It is, in fact, actually an integral part of the mucosa. In this illustration, also, it looks as though the nuclei had been dragged away by traction from the normal positions in the epithelium. (A. C. Hilding: *Ann. Otol., Rhin. and Laryng.*)

and in 15 per cent three courses were given.

The importance of infection accompanying the asthma was stressed and found present in 51 per cent of the series. Criteria for infection were elevation of the white blood count and purulent sputum rather than sputum culture. The accessory nasal sinuses were x-rayed routinely and irradiated if infected.

Results of 18 months' observation were 39 per cent excellent (almost com-



pletely relieved and without attack during 18 months); 40 per cent good (almost completely relieved but having occasional light attack requiring some

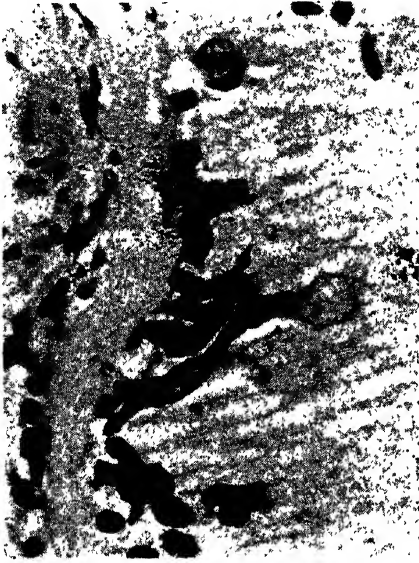


Fig. 25—High magnification of a field from Fig. 24. (A. C. Hilding: *Ann. Otol., Rhin. and Laryng.*)



Fig. 26—From the same patient as Figs. 24 and 25. Photomicrograph of another area of bronchial epithelium. Here some ciliated cells have been preserved. The mucus in the lumen appears to be free of the cilia, but is attached to epithelium in the secreting cells. The different appearances of the individual cells may be different stages in the metamorphosis. Note the differences in the ciliated plate, the protoplasm, and the nuclei in the numbered cells. (A. C. Hilding: *Ann. Otol., Rhin. and Laryng.*)

symptomatic therapy). Some of these required two courses of irradiation; 13 per cent fair (required three courses of irradiation, had some asthma most of the time and occasional hard attacks requiring adrenalin hypodermically); 6 per cent poor (not benefited objectively); 2 per cent, no results.

The dangers of preliminary fibrosis and skin burns are considered insignificant with these dosages repeated at three or four months' intervals. The annual amount could be repeated with safety for eight to ten years. The possible danger of irradiation of a patient who has had this therapy elsewhere is admitted.

Hilding<sup>32</sup> has pointed out the importance of ciliary insufficiency in fatal asthma. In one group, the autopsy material showed a metamorphosis of columnar epithelial cells into goblet-like cells, eventually rupturing, destroying the ciliated surface, and partially discharging their tenacious mucus which accumulated, plugging the air passages and producing asphyxia. The other group showed extensive sloughing of the bronchial ciliated epithelium in the presence of purulent fluids which collected and produced asphyxia, yet might have been removed had ciliary activity been intact.

In either case, *bronchoscopic removal of the secretions* is the only means of relief.

## PULMONARY TUBERCULOSIS

The increase in the incidence and mortality rates for pulmonary tuberculosis expected under wartime condition and realized in other countries,<sup>33</sup> has as yet not been evident in the United States. To the contrary, reports appearing during the year<sup>33, 34, 35</sup> show continuation of trend to decline observed in recent years. The probability of in-



crease the longer we are at war is anticipated by all. It is of interest here, however, to note that Robbins,<sup>36</sup> in following a group of 8731 relief individuals with normal chest x-rays (86.2 per cent Negroes) found the rate of incidence of pulmonary tuberculosis the same as in white groups on higher income levels. He reminds us that the annual incidence rate and mortality rate are entirely independent of each other and that their resultant is the prevalence rate. And that attempts to link these three factors by artificial formulae only lead to confusing and contradictory results.

Mass surveys, where possible, are the most effective means of control of epidemiology of tuberculosis and the chest x-ray is the most reliable single diagnostic procedure. Edwards<sup>35</sup> has suggested streamlining our procedure to conserve time and energy for the medical and nursing personnel sorely taxed by shortages in these times. He advocates surveys of groups which have shown most likelihood of infection and groups easily reached as:

1. Those unemployed—relief.
2. Negroes—due to rapid course and high death rate.
3. Medical students and student nurses.
4. Patients admitted to general hospitals.
5. Inmates of mental hospitals.
6. Prisoners.
7. Industry.
8. Applicants for civil service.
9. Colleges.
10. High schools.

Physicians are urged to co-operate fully with these programs, and the lack of funds furnished public health agencies for efficient service is decried.

An almost ideal program for diagnosis and control of tuberculosis in a group is demonstrated by the co-operation of the

Bureau of Tuberculosis of New York City with the army induction centers in that area. Ehrlich, Schiller, and Edwards,<sup>37</sup> analyzing the statistics for this group, found that out of 114,130 chest x-rays, 1304 (1.14 per cent) were rejected under M.R. 1-9; 1156 (1.01 per cent) were diagnosed chronic tuberculosis. Of this latter group, 435 (0.38 per cent) were clinically significant, and 721 (0.63 per cent) were arrested. The clinically significant cases were kept under surveillance of the chest clinics and treated according to indication. Of the chronic group, some were reclassified as fit for active duty; one-half as many were reclassified as fit from 14" x 17" paper films as from 4" x 5" regular film, indicating the necessity for conservatism in interpretation of the small films. In another report on the same subject, Edwards<sup>38</sup> states that 8 per cent of those rejected under M.R. 1-9 were returned as fit for duty. The elimination of those with known tuberculosis from the armed services is estimated to save the government \$13,000,000.<sup>31</sup>

Interesting observations in the physiologic changes in the breath sounds have been recorded and correlated with tuberculin reactions and x-rays by Ellison and Cohen<sup>39</sup> in 450 chest clinic children. Increase in intensity of breath sounds and prolongation of the expiratory sound over the right apex particularly is interpreted as pathologic rather than physiologic, as it has been usually considered in texts on physical diagnosis. Adequate aeration of the posterior superior portion of the lung is dependent on the normal downward and forward movement of the hilus in inspiration. Fixation of the hilus by tubercular primary involvement with tracheobronchial adenitis prevents this physiologic motion and produces a hypoventilation of the superoretro hilar region. This hypoven-

TABLE III\*  
SUMMARY OF 450 CASES

Group	Physical Signs	Tuberculin Reaction	X-ray	No. of Cases
1	Positive	Positive	Positive	158
2	Positive	Positive	Negative	75
3	Positive	Negative	Positive	54
4	Positive	Negative	Negative	79
5	Negative	Negative	Negative	34
6	Negative	Negative	Positive	12
7	Negative	Positive	Negative	17
8	Negative	Positive	Positive	21
				450

\* R. T. Ellison and J. Gershon-Cohen: Am. Rev. Tuberc.

tilation produces the changes in the breath sounds in the upper portions of the lung. Viscerosomatic reflexes are considered responsible for trophic changes in the musculature and subcutaneous tissues on the corresponding side. Eighty-five per cent of the cases with evidence of definite tubercular involvement by antero-posterior x-ray had positive physical signs.

Demonstration of tubercle bacilli by special examinations has been the subject of three reports during the year. Ordway, Medlar, and Sasano,<sup>40</sup> using concentration, culture, and pig inoculation and lavage when no sputum was available, found 35.4 per cent of 907 specimens positive from 99 cases with negative (smear) or no sputum; 76 cases were positive one or more times; 62 were positive only when 72-hour sputum or two lavages were done. Decker, Ordway, and Medlar<sup>41</sup> over a five-year period found 67 out of 97 patients with minimal active disease to have positive sputa. During the previous five-year period, when special procedures were not in vogue, only 24 positives were obtained on 172 patients. Gastric lavage produced bacilli in 41 of 56 "no sputum" cases. Sputum smears were posi-

tive on 16 of 269 cases. Foley and Andosca,<sup>42</sup> in 639 negative or no sputum cases, show 29.2 per cent positive by lavage. These various figures indicate the importance of special procedures from the standpoint of diagnosis, prognosis, infectiousness, and management of the particular case. To date, no culture medium has equaled the guinea pig.<sup>41, 42, 45</sup>

Knowledge of lability of the tuberculin reaction is not new, but two writings on this subject appearing during the year are worthy of comment. Pattenger and Pattenger<sup>43</sup> report 42 tuberculin positive children who became tuberculin negative on a building treatment for allergies, low energy, and delayed development. Therapy consisted of *good environment*, a potent *adrenal cortical extract*, *high protein and fat*, *low carbohydrate diet* with foods prepared with special attention to *preserving the natural vitamin content*.

In a group of 619 individuals over 65 years of age, Amazon<sup>44</sup> found that 22 per cent were inert to 0.1 mg. old tuberculin; 77 per cent of the latter were inert to 1.0 mg. O.T.; 37 per cent of the positive reactors had x-ray evidence of tuberculous infection; 36 per cent of the

nonreactors showed x-ray evidence of tuberculous infection.

These discrepancies illustrate the importance of routine roentgenologic chest studies whenever possible. Apropos of this are the observations of Farber and Clark<sup>46</sup> on 100 patients admitted to a general hospital for nontuberculous disease and later found to be tuberculous. Eighty-one per cent were advanced cases presenting a significant public health problem and hazard to the hospital personnel. A total of 1497 hospital days were spent by these patients before transfer to the tubercular wards and the median number of days, per patient, spent in the general wards was eight.

Where economics prevent routine x-rays, it has been suggested by Barrington and Greenwood<sup>47</sup> that routine blood sedimentation rates be used. When readings of 14 mm. per hour or over were obtained in the absence of other known infection, further tubercular studies were done in a mental hospital of 2000 inmates. They consider that clinically significant disease may be found and segregated by this method.

Treatment of pulmonary tuberculosis has shown no outstanding innovations in the past year. *Collapse therapy* holds main favor though it is of interest to note that it has shown a decrease in percentage usage in several sections of the country in recent years. Drolet,<sup>48</sup> in reviewing the statistics of 100 large tuberculosis hospitals and sanatoria in various sections of the United States and Canada for a five-year period, from 1937 to 1941, shows a decrease in collapse therapy in 1941 as compared to that used in 1937. Highest incidence of collapse therapy was in the west with 58 per cent of the hospital census on December 31, 1941, and the lowest in New York City at 30 per cent on the same date. *Phrenic nerve operations* numbered 120 per

1000 on December 31, 1937, and 111 per 1000 December 31, 1941. *Artificial pneumothorax* showed 528 per 1000 in 1937, 524 per 1000 in 1941, a decrease of 1 per cent. New York City showed a decrease in the use of pneumothorax of 24 per cent in 1941, as compared to 1937. *Intrapleural pneumolysis* 59 per 1000 in 1937, and 79 per 1000 in 1941 (increase of 34 per cent); *thoracoplasty* 3950 total in 1937 and 5189 total in 1941 (increase 22 per cent). *Pneumoperitoneum* and *oleothorax* were relatively little used, 10 to 1000 and 5 to 1000, respectively, for the five-year period. *Monaldi operations* total 295 and *lobectomies* 92 for the five years.

In 1934 an average of 20 per cent of all adults in American tuberculosis institutions had some collapse therapy. The peak of 51 per cent was reached in 1939, then receded to 48 per cent in 1941. Institutional mortality rate in 1941 was 19 per cent general with a low of 13 per cent in the west and a high of 26 per cent in New Jersey. Mortality for English tuberculosis institutions from 1934 to 1938 was also 19 per cent. The mortality ratio for tuberculosis hospitals and sanatoria has remained the same as for the whole period prior to collapse therapy. It is significant to note that between 50 per cent and 57 per cent of cases were admitted in far advanced stages which was also true in 1925. Drolet concluded from his survey that "the natural evolution of pulmonary tuberculosis continues unmodified." Also that the greatest value of hospital and sanatorium care is the segregation of infectious cases and prevention of spread in a community. Too many cases are admitted in the advanced stages and too many cases leave institutions against advice.

"In isolated selected instances certain surgical operations achieve remarkable

results and save a few lives; too often other collapse therapy measures unfortunately add complications to already serious cases; after care is a meaningless term at present to the majority of the discharged patients who too frequently must return to unfavorable living and working conditions."

These statistical facts make one wonder why we should continue with collapse therapy, but our experience tells us that there are other phases of tuberculosis statistics that are not mentioned by Drolet, and as Davidson<sup>49</sup> has pointed out, the mortality rate may be insignificant as compared with the number of individuals restored to health and their useful place in society.

Tice,<sup>50</sup> in reporting on ten years' experience with *ambulatory pneumothorax*, strongly advocates field pneumothorax as one of the best means of controlling infection from a public health standpoint. Of his 6481 cases, 34 per cent were ambulatory, 40 per cent combined ambulatory and sanatorium and 26 per cent sanatorium alone; 95 per cent of the group were classified as moderately or far advanced and 73 per cent had positive sputum. Results of the sanatorium group were better than the clinic group, but the combined sanatorium and clinic group were best of all. From survival and sputum conversion, *thoracoplasty* outranked all other procedures in efficacy.

*Pneumothorax* in Negroes, as observed over a nine-year period has been reported by Hoffman.<sup>51</sup> Contrast of a group with effective pneumothorax against a group with ineffective pneumothorax is made. His definition of effective pneumothorax as that giving "sputum conversion abatement of clinical symptoms, and radiographic evidence of cavity closure" should conclude good results in this group.

The series was made up of 12 patients with minimal unilateral, 246 with moderately advanced (209 unilateral) and 100 with far advanced disease (47 unilateral).

Three hundred and thirteen unilateral and 45 bilateral pneumothoraces were induced in 358 patients. Adhesion accompanied 90.5 per cent of the cases and prevented effective collapse in 83.4 per cent. Of the 313 unilateral pneumothoraces, 43 (13.7 per cent) were effective; 109 (34.9 per cent) were rendered effective by close pneumonolysis; 161 (51.4 per cent) were ineffective or remained ineffective after incomplete pneumonolysis. Of 45 bilateral pneumothoraces, 20 per cent were effective or rendered effective and 80 per cent remained ineffective.

Of the 152 effective unilateral pneumothoraces, 71.1 per cent were discharged, 6.6 per cent left against advice, and 22.3 per cent died.

Of 161 ineffective unilateral pneumothoraces, 34.2 per cent were discharged, 12.4 per cent left without approval, and 53.4 per cent died.

Of 45 bilateral pneumothoraces, 20 per cent were discharged, 6.7 per cent left without approval, and 73.3 per cent died.

*Diaphragmatic paralysis* for closure of tuberculous cavities has been discussed by Ellison and Tittle.<sup>52</sup> The procedure effected closure of right apical cavities in 50 per cent of their cases and left apical cavities in 33 per cent. Closure on the right frequently followed an atelectasis of the upper lobe and a fanning up of the lobe against the upper mediastinum. This type of closure was not observed on the left and may account for the better results on the right (Figs. 19 and 20).

The physics involved: "The musculature of the diaphragm is in a constant state of tension even when not actively

contracting and this force opposes the elastic recoil of the lungs and keeps the pulmonary tissue continually on a stretch. The diaphragmatic musculature also opposes the positive intra-abdominal pressure created by contraction of the muscles of the abdominal wall and prevents the transmission of this pressure to the contents of the rigid thoracic cage. When one-half of the diaphragm is paralyzed it rises into the thorax because of the pull of elastic tissue from above and, especially with pneumoperitoneum, because of a positive push from below. The effect of this on cavities depends on their location. If the cavity is in the lower two-thirds of the lung, there is usually a considerable amount of resilient lung substance on all sides of it, and closure is chiefly the result of relief of outward pull of elastic tension on its walls. If the cavity is in the apex, however, there is less resilient lung above it and the loss of tone of the diaphragmatic muscle allows the positive intra-abdominal pressure to neutralize the entire elastic recoil of the lung on that side. There is then a positive pressure in that half of the thoracic cage and the cavity is forced against the rigid walls of the cupola of the thorax.

"This concept offers an explanation of the successful closure of apical cavities following diaphragmatic rise, but it does not help to explain why the results are more satisfactory in the right apex. The answer to this problem might be found in a consideration of the anatomical differences in the two sides. The anatomy of the right hilar region differs from that of the left in at least three respects. First, the angle that the right mainstem bronchus makes with the line of the trachea is much greater than that formed by the left mainstem bronchus. Second, the relation of the bronchi to the pulmonary blood vessels differs on the

two sides. The bronchus to the right upper lobe rises above the point where the pulmonary artery crosses the mainstem bronchus, being termed the eparterial bronchus. On the left, the mainstem bronchus does not divide until beyond the point of crossing of the artery. Third, there are more lymphatic nodes about the right hilum and especially the upper lobe bronchus, than there are on the left side. As a result of these anatomical peculiarities, it is our belief that a marked rise in the diaphragm on the right side frequently leads to a kinking or pinching off of the eparterial bronchus, resulting in atelectasis of the right upper lobe and in this way closure of the cavity. Thus, the mechanism of direct pressure and the closure of the eparterial bronchus help to explain the successful effect of diaphragmatic rise on lesions in the upper right lung."

Factors contributing to unsatisfactory results of this procedure in the right lower lobe are discussed.

"First is the fact that without counterpressure a cavity in either lower lobe may ride up on the elevated diaphragm like a bubble on a wave, without any reduction in size. Second, when the diaphragm rises following paralysis, it is only a further stretching upward of the dome above its attachments, these attachments remaining immobile. This results in exaggeration of the normal triangular space lying behind the dome of the diaphragm. If the lung is adherent to the sides of the costophrenic sulcus, it cannot escape from this triangular space as it normally does during expiration, and little or no effect is noted on cavities lying in this portion of the lower lobe (Figs. 30 and 31). There is one other factor that makes the right lower lobe the most unfavorable site of all. When viewed in a true lateral projection, it is evident that the apex of the

Fig.  
27Fig.  
28Fig.  
29Fig.  
30Fig.  
31Fig.  
32

Figs. 27 and 28 (first row)—Case 1. Phrenic exeresis performed January 10, 1931, in an attempt to collapse a cavity lesion of the right upper lobe. Fig. 27 shows an immediate satisfactory rise in the diaphragm with the cavity still open. X-ray film on April 15, 1931 (Fig. 2), shows cavity closed and upper lobe compressed fanlike against the mediastinum due to atelectasis and/or fibrosis.

Fig. 29 (middle left)—Case 2. Cavity in the right lower lobe which has "ridden up" on a paralyzed diaphragm, failing to collapse even after the addition of pneumoperitoneum.

Fig. 30 (middle right) and Fig. 31 (lower left)—Case 3. Phrenic crush on the right side in July, 1939, for tuberculous cavity in right lower lobe, followed by pneumoperitoneum 3 months later. X-ray film taken September 30, 1939 (Fig. 30) shows cavity not influenced by a satisfactory rise of the diaphragm. In a lateral view (Fig. 31) the cavity is seen to be located in the triangular space behind the dome of the diaphragm, and the apex of the dome of the paralyzed right diaphragm is anterior to the vertical plane through the hilum.

Fig. 32 (bottom right)—Case 4. Left phrenic crush done January 1, 1939, followed by induction of pneumoperitoneum for tuberculous infiltration in the left upper lobe. The posteroanterior view shows satisfactory rise in the left diaphragm. The lateral view (Fig. 32) shows how the heart lies in front of the dome of the left diaphragm, the apex of the dome lying behind the midline and that the posterior triangular area is obliterated. (R. T. Ellison and C. R. Tittle: *Am. Rev. Tuberc.*)

dome of the diaphragm on the right side is anterior to the vertical plane through the hilum (Fig. 31). On the left side, however, the heart lies in the anterior half of the chest and the diaphragm has to pass under it before it can begin any appreciable rise. This pushes the apex of the dome behind the midline, thereby reducing the size of the triangular space behind the left diaphragm."

**Chemotherapy** in tuberculosis remains in a somewhat experimental stage. The **sulfonamide compounds** have shown little or no results in some groups<sup>64</sup> and have given encouraging results in others. Hinshaw, Pfuetze, and Feldman<sup>53</sup> and Heaf, *et al.*,<sup>54</sup> reported on the use of **promin** in a series of 106 cases of tuberculosis. Thirty-six of these received what was considered an adequate therapeutic trial. The most favorable results were obtained on patients with exudative lesions without much tissue destruction and without extensive fibrosis; 39 per cent obtained reversal of sputum to negative. Cavity closure occurred in 28 per cent. The blood sedimentation rate improved in 70 per cent. Of four mortalities, three were in terminal stages before therapy was begun. Six tuberculous meningitis cases were all fatal. In two of these, chemotherapy had been started in an early phase. These authors were favorably enough impressed with promin to urge its further use in larger series, particularly in cases with exudative lesions.

Nutritional studies in tuberculosis have been directed toward the **vitamins**. The plasma content of **vitamin A** and **ascorbic acid** was determined by Getz and Koerner<sup>55</sup> in clinic patients of the lower economic group. Two hundred and sixty-five subjects were tested, including 27 staff members who served as controls. The measurement of the Carr-

Price reaction by the Evelyn photoelectric colorimeter was used for vitamin A and recorded in international units per 100 cc. of plasma. Plasma filtrate reduction of 2.6 dichlorophenolindophenol was used to determine the amount of ascorbic acid in milligrams per 100 cc. of plasma.

Standards for vitamin A in males were normal 110 and above, borderline 85 to 110, and pathologically deficient below 85.

Standards for females were: Normal, 95 and above; borderline, 75 to 95, and pathologically deficient, below 75.

Standards for ascorbic acid were: Minimal normal, 1 mg. per 100 cc. plasma; pathologically deficient below 0.5 mg. per 100 cc. of plasma.

None in the control group were found pathologically deficient for vitamin A.

The white nontuberculous group showed 28.1 per cent borderline and 12.5 per cent deficient in A.

White tuberculous patients, just diagnosed, showed 30.7 per cent borderline, and 30.7 per cent deficient in A.

Negro nontuberculars gave 37.6 per cent borderline and 28.5 per cent deficient in A.

Negro tuberculous, just diagnosed, gave 13.3 per cent borderline and 80 per cent deficient in A.

Of just diagnosed tuberculous patients, according to extent of involvement, minimal cases showed 35.7 per cent borderline and 35.7 per cent deficient. Moderately advanced borderline were 20 per cent and deficient 60 per cent. Far advanced cases were 100 per cent pathologically deficient in vitamin A.

A significant difference in ascorbic acid levels in the plasma were noted in males (0.17 mg. per cent) and females (0.42 mg. per cent) and in whites (0.47 mg. per cent), and Negroes (0.21 mg. per cent). The tuberculous group were



uniformly low in ascorbic acid, and in a number of instances none could be detected in the plasma. Due to the low readings and the small number of active cases, no relation could be drawn between ascorbic acid content and the stage of the disease.

The clinical significance of these findings is as yet not known. It is quite possible that correction of such deficiencies might increase the resistance to tubercular infection and increase the ability to heal the disease.

Another paper was written by McConkey<sup>56</sup> on the administration of 3 oz. of *tomato or citrus fruit juice* with a  $\frac{1}{2}$  oz. of *cod-liver oil* after meals as a sanatorium routine. By this the incidence of laryngeal tuberculosis as a complication has been reduced from 3.3 per cent to 1 per cent. The complication of intestinal tuberculosis shows a reduction from 11 per cent to 1 per cent on the same routine. Patients under collapse therapy were purposely omitted from his observed series.

Prognosis in tuberculosis is always difficult to judge with any consistent degree of accuracy except possibly in the worst of the far advanced group. For minimal pulmonary tuberculosis, the prognosis is considered usually good and this is substantiated by mortality rates in sanatoria. The seriousness of minimal tuberculosis among individuals who for economic or other reasons do not fall into this special sanatorium group is vividly demonstrated in the analysis of 66 such cases by Stein and Israel.<sup>57</sup> The period of observation ranged from one to five years with a mean of 30.8 months. At the end of this period, the white cases showed 50 per cent stable or retrogressive; 13 per cent indeterminate; 31 per cent alive with progressive disease, and 6 per cent dead. Of the colored group, 48 per. cent were

stable or retrogressive; 4 per cent indeterminate; 26 per cent alive with progressive disease, and 22 per cent dead. These figures justify the authors' appeal for adequate sanatorium facilities with prolonged and intensive treatment.

Bronchspirometry has contributed much to our knowledge of respiratory physiology and disease. Suffice it here to mention a relatively simple and practical application of this procedure which should be particularly helpful in tuberculosis as an indicator for or against collapse procedures. Steele<sup>58</sup> points out that the equipment necessary is a bronchspirometry catheter and two basal metabolism apparatuses, one to be connected to each side of the double channeled catheter. He reiterates that the oxygen consumption is the most important and constant factor in determining the functional capacity of a lung. This can easily be determined in liters of oxygen per minute for each lung with the apparatus mentioned and without the aid of the laboratory. Steele demonstrates the application of this by citation of three cases, the summaries of which follow:

A 27-year-old woman required thoracoplasty for disease of her right lung. A 50 per cent pneumothorax collapse of the left lung was present. Vital capacity was 1000 cc. X-ray revealed some aeration of the right lung, but bronchspirometry showed practically no oxygen consumption on this side. "The left lung, partially collapsed by pneumothorax, was carrying practically the entire respiratory load." Right thoracoplasty was successful and probably would not have been done if bronchspirometry had not been favorable.

A 27-year-old female presented a similar indication for right thoracoplasty. Vital capacity was 900 cc. A 40 per cent left pneumothorax collapse was present. "Bronchspirometry revealed practically equal oxygen consumption on both sides. Thoracoplasty contraindicated."

A 49-year-old woman had a large tension cavity in the left apex. Cavity drainage and thoracoplasty appeared needed. Vital capacity

1000 cc. Bronchspirometry showed the left lung functionless. Preliminary anterior thoracoplasty, Monaldi cavity drainage, and an eighth rib posterior thoracoplasty were performed without incident.

## PNEUMOCONIOSIS

This malady has been recently, lucidly, and comprehensively discussed by Haythorn.<sup>59</sup> Lungs sent to this laboratory for confirmation of the diagnosis of silicosis showed it absent. The diagnosis had been mistakenly made on shadows cast by the following: Tubercles, miliary abscesses, nodules of organizing pneumonia, fibrosis due to chronic passive congestion, and by primary carcinoma.

Under pathogenesis he considers the pneumoconioses to include varying degrees of fibrosis of the lungs due to inhalation of dust particles under 10 microns in diameter. The larger particles are disposed of by the protective mechanism in the upper tracts and do not reach the air sacs. Silica and mixtures of silica with other dusts produce the greatest fibrosis but fibrous proliferation (reticulation) has been experimentally produced by inhalation of soft coal smoke.

Steps in development consist in the phagocytosis of the particles in the lung alveoli and the transportation by cells through the alveolar walls and lymphatics to nearby lymphoid collections where, in the case of more inert dusts, they persist indefinitely. Fibroblasts about them proliferate and produce fine reticular strands of collagen. In case of mixed dusts, the degree of reticulation is proportional to the amount of dust and the percentage of silica. The process may be arrested at this point and remain as reticulation. This is the usual final stage in soft coal miners and in nonindustrial anthracoses.

Where silica concentrations are high, the phagocytes collect in aggregate, break down, and their contents are passed to other phagocytes in the borders of the necrotic foci. Each necrotic focus undergoes fibrous replacement with the production of wide lamellae of collagen and the typical silicotic nodule is formed. The early nodules are discrete entities, but are numerous and scattered widely throughout all portions of both lungs. The process may remain here as "nodular silicosis." If it advances, small groups of nodules fuse to form conglomerate ones of considerable size. In the final stages, conglomerate nodules become united by fibrous bands which cause collapse of the air sacs between them and in the end lead to large, nonair-containing fibrous masses. This stage is "massive silicosis."

Emphysematous bullae occur in all types of pneumoconiosis. The outer walls of these bullous spaces become stiffened and inelastic and do not expand and contract as normal lung tissue. Arteriosclerosis, almost always an accompanying change, completes the pathologic background for clinical emphysema.

Tuberculosis and silicosis are very commonly associated. The typical lesions of both conditions are the result of progressive necrosis and fibrous repair. Belt is quoted as follows:

"It is not a question of tuberculous infection being simply a parallel of the pneumoconiosis; on the contrary, the two processes combine to form lesions which are distinctive neither of dust alone nor of tubercle alone. . . . It is almost inevitable, therefore, that the two should overlap. But the result is a good deal more than a simple overlapping; it is as if the pathogenicity of the tubercle were altered by the silica and the silica altered by the tubercle, with the result

that more fibrosis is produced than would be expected by either alone."

Haythorn, in discussing the pathology of the lungs, calls attention to the fact that any "gritty feel" encountered by the fingers or the knife is calcium in either an old tubercle or in an athermatous cyst or plaque and not from the silicosis.

The importance of history of employment and the duration of exposure to silica-containing dusts are stressed and the general consensus repeated that clinical disease is unusual with exposure of less than ten years.

Mention is made of the clinical improvement in patients treated with *aluminum inhalation* and, while no explanation of the pathologic physiology is offered, Haythorne commits himself definitely against the theory of desquamation of the thickened alveolar epithelium.

The dust hazard in tremolite miners and millers are reported by Seigal, Smith, and Greenburg.<sup>60</sup> About 65 per cent of the world's supply of tremolite talc is supplied by the United States. Deposits are in Vermont, New York, California, North Carolina, and Georgia. The talc is hydrous magnesium silicate,  $H_2Mg_3(SiO_3)_4$ . Dust counts in the mines were 6 million to 5000 million per cubic foot. Dust counts in the milling ranged from 20 million to 215 million per cubic foot.

Of 221 workers x-rayed, 32, or 14.5 per cent, showed pulmonary fibrosis. These 32 cases were all from a group of 107 men who had worked in the industry ten years or longer, giving a 29.9 per cent of fibrosis from this group. Of eight men employed 30 years or more, six, or 75 per cent, had fibrosis; 6.3 per cent of the whole group had plaques at the periphery of the fields. These were called talc plaques and were

apparently independent of other lung pathology.

The fibrosis appeared as a fine diffuse granulation or nodulation on a clear background. Accompaniment of symptoms of dyspnea, cough, and fatigue were frequent and often disabling.

Of 18 cases of fibrosis without exposure to any other dust than talc, three cases showed concomitant tuberculosis.

## SPONTANEOUS PNEUMOTHORAX

The majority of spontaneous pneumothoraces have been attributed to rupture of tuberculous foci. Stein, McConkie, and Kuehn<sup>61</sup> report five cases occurring in apparently healthy soldiers in whom no tuberculosis could be found. Four of these occurred during some physical effort, while the fifth occurred while the individual was at complete rest. The etiologic factor in these cases was assumed to be the rupture of an emphysematous bleb.

In reviewing the pertinent literature, they cite larger series of similar cases previously reported and classification of etiologic factors are as follows: (1) Rupture of a tuberculous focus; (2) rupture of a pleural adhesion; (3) rupture of an emphysematous bleb, and (4) presence of a pleural defect.

The incidence, based on 49,198 chest examinations, was 0.11 per cent, with males predominating two to one, according to Santos and Tanchanco.

Pathogenesis as classified by Ehrlich and Schomer was used as follows:

1. The *open type* is that in which air enters and leaves the pleural cavity through the point of rupture in the lung during respiration. The air in the pleural cavity overcomes the negative pressure and the lung collapses. The quantity of air in the pleural cavity, however, re-

mains stationary until absorption of this air commences, whereupon the tear in the pleura heals.

2. The *closed type* is that in which a rupture of the pleura results in a quick sealing of the lung. The amount of air in the pleural cavity varies, depending on the size of the tear and the positive pressure necessary to collapse the lung.

3. In the *valvular type*, the air gets in but cannot get out, causing tension pneumothorax.

Spontaneous interstitial pneumothorax, as described by McGuire and Bean, is also mentioned. It involves escape of air through ruptured alveoli or bronchioles into the interstitial tissues of the lung. The air may either extend toward the hilum and enter the mediastinum or extend toward the pleura, where vesicles develop, causing a rupture and spontaneous pneumothorax.

Treatment by *rest in bed* for four to six weeks and *general supportive measures* is in vogue. *Aspiration* should be done only in tension pneumothorax. High altitudes should be avoided. Strenuous physical exertion should be avoided to prevent recurrences.

## EMPHYEMA

Clagett and Shepard<sup>62</sup> have reviewed the records of 346 cases of chronic empyema in an effort to learn the causes of chronicity and to determine the methods used in its eradication in these cases.

The incidence has shown a relative decrease in recent years. It is not a disease but a complication of another disease. In this series, it occurred following pneumonia, influenza, pleurisy, tuberculosis, trauma, and the acute exanthemata in the order named.

The most common causes of chronicity were: (1) Inadequate drainage; (2) tuberculosis; (3) too late drainage; (4) bronchial fistula, and (5) bronchiectasis.

"Prophylaxis of chronic empyema is the establishment of early adequate drainage in every instance of acute empyema."

"An effort should be made to determine the bacteriologic characteristics of the (chronic) cavity, and if there is a thoracic sinus, a piece of thickened pleura should be obtained for biopsy for the detection of evidence of tuberculosis; if the *Myco tuberculosis* is obtained by culture, smear, or biopsy, or if tuberculosis is proved by inoculation of guinea pigs, a less conservative surgical procedure should be anticipated, for . . . tuberculous empyema does not respond well to conservative measures. A search should be made for bronchial fistula, and if one is found it should be repaired as an aid to early obliteration of the cavity. Frequent determinations of the size of the cavity should be made and recorded, so that it can be determined whether or not it is decreasing. The most simple method of measurement of the size of a cavity is determination of the amount of fluid required to fill it. Roentgenograms of the cavity should be made occasionally (and with the aid of radio-opaque oil) so that its shape and extent can be determined. If conservative treatment, such as *irrigation with Dakin's solution* and *minor plastic surgical procedures* on the wound, does not cause a decrease in the size of the cavity, more radical procedures, such as *unroofing of the cavity* or even *thoracoplasty* should be considered." (Further surgical discussion is omitted.)

Deaths in the hospital after operation (18) were due to operative shock and spread of the infection by contiguity or metastasis (the most common form of the latter was abscess of the brain). Nonfatal complications were thoracic sinus, exacerbation of coexisting nephri-

tis, metastatic infections, and tuberculosis of the spinal column.

There were 35 deaths which occurred at the patients' homes among 212 answers to inquiries. "Many of these 35 patients died of causes entirely unrelated to the empyema." One hundred and sixty-four patients stated that their health was excellent and that they had been able to resume their usual mode of life.

### ATELECTASIS

This condition as a complication of surgery or anesthesia or both has frequently been diagnosed postoperative pneumonia. If untreated, it usually eventually does assume a pneumonic state. Papers on the subject have appeared by Schotz<sup>63</sup> and by McIver and Seabaugh.<sup>64</sup> Both papers advocate the withholding of surgery until the respiratory tract can be cleared of any existing infection or tenacious secretions; also, sedation or narcosis preoperatively and postoperatively due to its paralytic effects on pulmonary movements and the action of the tracheobronchial mucosal cilia. Maintenance of free air passage during anesthesia, by aspiration if necessary, is most essential. "Stir up" routine of frequent turning, deep breathing, and cough, if secretions are present, is encouraged. *Atropine* for bronchial dilatation and to subdue secretions is advocated by Schotz, but McIver and Seabaugh speak against this drug as rendering the bronchial mucus too tenacious and difficult to raise.

Given atelectasis not relieved shortly by simple methods, *bronchoscopy* is indicated.

### PULMONARY EDEMA

Drinker and Warren<sup>65</sup> have pointed out the probability of low pulmonary capillary pressure (5 to 10 mm. Hg.)

due to the magnitude of the capillary bed and the resilience of the lung tissues. Osmotic pressure of the blood flowing through the lungs is higher than the capillary blood pressure. Any impediment to inspiration or severe respiratory movement which increases negative pressure within the chest will favor pulmonary transudates.

Anoxia increases the permeability of the pulmonary capillaries in favor of leakage.

Experimental impediment to inspiration produced these two factors and increased lymph flow (right lymphatic duct) from 11 mg. per minute to 82.5 mg. per minute.

Irritants, as gases, viruses, or bacteria, cause exudates from pulmonary capillaries. Clotting of these exudates renders lung function worse than when the simple transudates are present, as the former are not as easily removed. If cell destruction by the irritant is not too great, coagulation may be slight and the exudate will be efficiently removed by the lymphatics.

An experimental animal (or individual in warfare) may inhale lethal amounts of gas and show no serious signs for several hours after. Then he may drown in his own exudates which eventually accumulate and clot, due to cell damage. Though the capillaries are damaged to the point of leakage, they do not fail to conduct blood. The failure is in oxygenation which may be combated by early *use of pure oxygen*, preferably under pressure.

Clinical experience has taught that when the physician decides that a patient needs oxygen, he is about 12 hours too late. When capillary leakage is pronounced, it is difficult to reverse.

The question of pulmonary edema has been approached from another angle by Luisada.<sup>66</sup> He considers that pulmo-

nary edema (not cardiac failure) is the result of acute congestion of pulmonary vessels followed by transudation in the alveoli, the immediate cause being stimulation of the vasodilators of the lung, due either to a lesion in the nerve centers or to visceral reflexes.

The edema following skull injuries, with subarachnoid hemorrhage, and in poliomyelitis is of the central type. Drowning and gassing are of the reflex type. Hypertensives probably have a multiple reflex by stimulation of receptors in the aortic arch, the carotid sinus, and the heart wall.

Luisada objects to *stimulant therapy* in pulmonary edema for three reasons.

1. *Digitalis* and *strophanthin* stimulate the right ventricle and increase the pressure in the lesser circulation, and by stimulating the vagus encourage narrowing of the coronary vessels.

2. Drugs stimulating the vasomotor center tend to increase the peripheral resistance and thereby increase the left ventricular failure and edema.

3. Drugs stimulating the respiratory center increase the frequency and depth of respirations and may increase the intrapulmonary negative pressure and favor transudation.

Luisada's recommendations for treatment embody having on hand ampules of *morphine*, 10 mg.; *atropine*, 0.5 mg.; *sodium phenobarbital*, 30 mg., and *distilled water*, 10 cc.

In hypertension, aortic regurgitation, aortitis, and toxemia of pregnancy, *morphine plus papaverine plus atropine* is the best combination.

For inhalation of toxic gases, skull injuries, drowning, and diseases of the central nervous system, *morphine plus atropine plus phenobarbital* is best.

If intravenous therapy is impracticable, the combinations may be given undiluted hypodermically.

If the intravenous injection is not successful after 15 minutes, *venesection* may be useful. If no relief is obtained by this, repetition of the injection is recommended in another ten minutes.

Venesection is contraindicated in coronary thrombosis.

The value of *oxygen* is mentioned.

Other chemotherapeutic agents and *penicillin* and related substances<sup>67-70</sup> of quite probable value in respiratory diseases are not generally available and have been purposely omitted here.

Likewise carcinoma, cysts, abscesses, and their treatment have been left to the realm of surgery until further medical therapeutic developments may change their distribution.

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## TROPICAL MEDICINE

WILLIAM SAWITZ, M.D.

### MALARIA

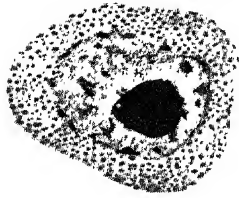
Malaria constitutes the major health problem in tropical and subtropical areas of the world. At the present time, the movements of large groups of individuals into highly endemic areas and their return make the malaria problem still more complex. In the United States the malaria mortality rate appears to have de-

creased<sup>1</sup> within the last decades, although in waves. It will depend on the efficiency of the control measures taken whether this favorable trend will continue.

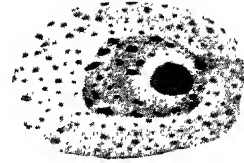
### Causative Agents

The organisms causing malaria belong to the *Plasmodia* and the species recognized as infecting man are:

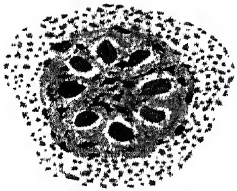




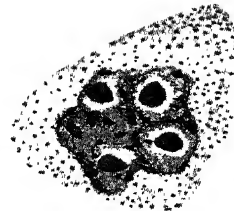
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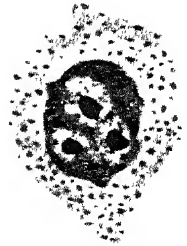
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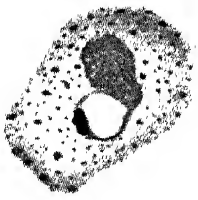
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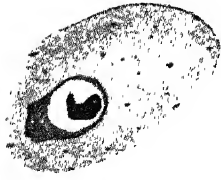
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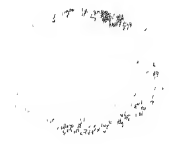
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PLASMODIUM OVALE

M. H. Springer, '43

1. Normal erythrocyte ; 2, 3. Trophozoites ; 4, 5, 6. Schizonts ; 7, 8. Gametocytes.



1. *Plasmodium vivax*, the causative organism of tertian malaria. It completes its erythrocytic life cycle within 48 hours, each time dividing into about 20 merozoites (μέρος = part).

2. *Plasmodium malariae*, the causative organism of quartan malaria. It completes its erythrocytic life cycle within 72 hours, each time dividing into about ten merozoites.

3. *Plasmodium falciparum*, the causative organism of estivoautumnal or malignant or subtertian malaria. It completes its life cycle within 30 to 48 hours, each time dividing into about 25 merozoites.

In addition to these three well-known human *Plasmodia* a fourth one has been accepted as a separate species:

4. *Plasmodium ovale*. It completes its life cycle within 48 hours, each time dividing into about ten merozoites. It causes a tertian malaria.

This organism was first described by Craig in 1900, but not named, and re-described by Stephens in 1922. Several authors since then have confirmed it to be a valid species. It has maintained its morphological characteristics through several passages through humans as well as mosquitoes.

**Geographic Distribution of *Plasmodium Ovale***—*P. ovale* has so far been reported from the Philippines, China, India, Russia, Iran, Palestine, Mauritius, East Africa, and South America.<sup>2</sup>

**Morphology**—*Plasmodium ovale* resembles morphologically *P. malariae*, while the 48-hour completion of its life cycle and the changes it produces in erythrocytes resemble *P. vivax*.

The trophozoite stage appears similar to *P. malariae*, but the parasitized erythrocyte is somewhat enlarged, usually oval in shape, and shows large Schüffner's dots which are formed very early.

The schizont, oval or round in shape, fills about half of the erythrocyte. The *Plasmodium* divides into six to 12, usually eight, merozoites, which have brown pigment in the center. The erythrocyte is somewhat enlarged, oval or round, and shows large Schüffner's dots.

The gametocyte fills about two-thirds of the erythrocyte, which is oval or round in shape and usually irregular in outline. It shows numerous large Schüffner's dots.

#### **Life Cycle of Malaria Plasmodia—**

The sexual cycle of human malaria *Plasmodia* in mosquitoes has been known since 1898. It has been known that the female *Anopheles* inoculates the infective stage, the sporozoite, into man while she takes a blood meal. According to Schaudinn's report (1902), such sporozoites inoculated into the circulation invade erythrocytes, where they start the asexual, erythrocytic multiplication phase. It was believed that the incubation period in malaria of about 13 days was needed for the erythrocytic forms to increase to a level sufficiently high to produce fever paroxysms. Progress in our knowledge made in the last decade does not bear out this direct sporozoite-erythrocyte invasion to be true. A rather important new concept of an additional life cycle in nonerythrocytic cells of the human host has been accepted on the basis of a number of experiments and experiences.

**The Asexual, Exoerythrocytic Cycle of Malaria Plasmodia**—Numerous attempts have been made to duplicate Schaudinn's observation, who saw, he claimed, sporozoites invade erythrocytes in a wet film. None of the experiments has met with success, and Boyd and Stratman-Thomas (1934) have disproved it as much as any experiment with a negative result can possibly disprove a positive statement. These au-

thors let infective mosquitoes "bite" a blister produced by cantharides in a susceptible human being. A typical malaria infection resulted. When erythrocytes were introduced into the blister and sporozoites inoculated into the blister fluid, the erythrocytes did not "trap" the sporozoites, but an infection resulted just the same.

Since the onset of fever paroxysms depends on the number of parasitized red cells, it should be possible to shorten the incubation period by the inoculation of a very large number of sporozoites. However, actual experiments showed that the incubation time remained the same regardless of the starting number of sporozoites. Moreover, blood taken during the first eight days after inoculation even in large amounts failed to infect susceptible individuals, suggesting that erythrocytic stages were absent in the circulation at this time. Further information was gained from the study of malaria in experimental animals. In birds infected with bird malaria, spleen, bone marrow, and brain<sup>3</sup> were found infective during the early incubation period, when the blood was not yet infective. Direct examination revealed the presence of dividing stages of *Plasmodia* in reticuloendothelial cells. In these cells, the malaria pigment, hematin, was absent, further proof that development had taken place in cells without hemoglobin content.

Studies of these stages in the reticuloendothelium of birds by several investigators<sup>4</sup> showed that the schizogonic development took place with the same regularity and at the same intervals as is known from the stages within erythrocytes.

These forms in the reticuloendothelial system have been named exoerythrocytic stages by James and Tate, reticuloendothelial forms by Raffaele, endothelial

stages by Kikuth,<sup>5</sup> and cryptozoites by Huff *et al.*<sup>4</sup>

The cryptozoites do not develop at equal intensity in all the cells of the reticuloendothelium. In bird malaria they have been found in reticuloendothelial cells of the brain, lung, spleen, bone marrow, heart muscle, kidney, adrenal, ovary, and intestine, but the distribution appears to vary with different species. The quantitative distribution has been investigated in quite a number of avian *Plasmodia*.<sup>6</sup> Although the distribution in man is not yet known, cryptozoites of three human malaria species have been demonstrated. In 1937, Raffaele found unpigmented schizonts of *Plasmodium vivax* in the bone marrow, and in 1940, of *Plasmodium malariae*. In 1939 Cassini saw unpigmented stages of *Plasmodium falciparum* in bone marrow smears.

It appears that the initial cryptozoite cycle in the reticuloendothelium is obligatory for the sporozoites before some of the cryptozoic merozoites are capable of invading erythrocytes to start the well-known cycle there. In addition to this initial involvement of the reticuloendothelial system, the phagocytic cells play an important part in cleansing the circulation of parasitized red cells, thus controlling the unlimited multiplication of the pathogens. Phagocytosed red cells are destroyed together with the parasites within the red cells, but there is some evidence that free merozoites, when engulfed by macrophages, are capable of continuing their life cycle. It has not been explained yet why the reticuloendothelial system serves as suitable medium for some malaria stages, while for others it means destruction. The sporozoite forms differ antigenically from erythrocytic stages. In the experiments of Russell *et al.* (1927) the injection of a suspension of dried sporozoites of *P. gal-*

*linaceum* (chicken malaria) resulted in a high sporozoite agglutination titer, and the birds contracted only a mild infection when inoculated by an infective mosquito. However, there was no protection against the intravenously inoculated erythrocytic stages.

From the results of these investigations it appears justified to diagram the life cycle of malaria *Plasmodia* as follows:

lial system explains the "hidden" reservoir of *Plasmodia* in individuals whose circulation is found free of *Plasmodia* and yet show a recurrence or relapse later on.

While *quinine* as well as *atabrine* are quite efficacious in destroying erythrocytic stages of *Plasmodia*, they appear to have no effect on cryptozoic stages. It is this drug-resistant cryptozoic stage that is responsible for the inefficiency of

## MALARIA PLASMODIA LIFE CYCLE

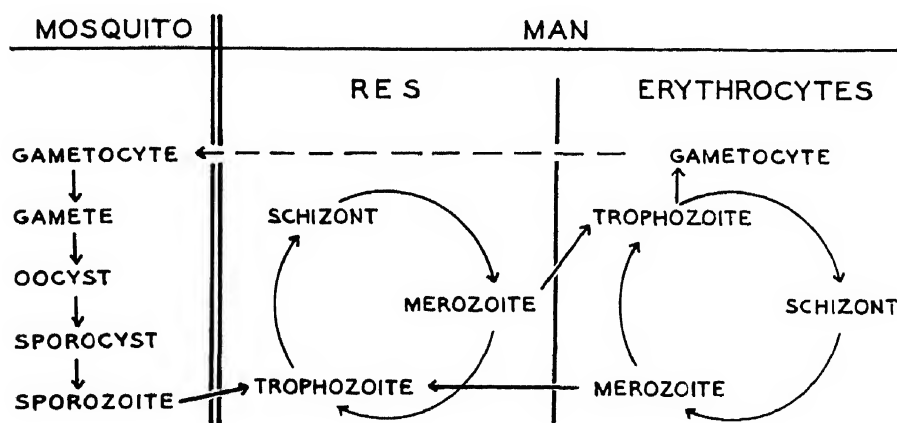


Fig. 1.

**Clinical Implications of the Cryptozoite Cycle**—The initial involvement of the reticuloendothelium results in an increased activity of these cells producing clinical manifestations which resemble other infectious diseases with reticuloendothelial involvement, particularly typhoid. The diagnosis of "typhomalaria" made by physicians of the last century on the basis of clinical manifestations has thus at long last been justified on a pathological basis. The primary as well as the secondary involvement of the reticuloendothelium explain the enlargement of those organs in which these cells are most prevalent. The cryptozoite phase in the reticuloendothe-

prophylactic treatment, and the prevention of relapses. Quinine and atabrine do not prevent infection, but they suppress clinical manifestations.

**Animal Reservoirs of Malaria Plasmodia**—It has been customary to state that no animal reservoir exists for the human malaras. Man alone has been considered responsible for the maintenance of endemic malaria. Rodhain's<sup>8</sup> experiments show that further investigation on this point is needed. He injected *Plasmodia* of apes into humans. Apes have been found infected with *P. schwetzi* which is similar to *P. vivax*, *P. rodhaini* which is similar to *P. malariae*, and *P. reichenowi* which is simi-

lar to *P. falciparum*. Rodhain inoculated paretics with *P. schwetzi* and from the human blood he recovered *Plasmodia* indistinguishable from *P. vivax*. Four paretics inoculated with *P. rodhaini* developed infections indistinguishable from *P. malariae*, and these were successfully passed to other humans. The epidemiological implications of these experiments are rather important, but they need confirmation.

### Clinical Manifestations

The typical fever paroxysms in malaria are well known and are seen particularly in induced malaria. In naturally acquired malaria, however, in relapses, and especially in partially treated patients the fever curve rarely assumes the typical curve. Birks<sup>9</sup> calls attention to the protean nature of malaria symptoms. In addition to the acute febrile forms, clinical manifestations without fever were observed, such as pains in the back, rheumatic pains about joints, pain in testicles, urticaria, multiple conjunctival ecchymoses, cardiac irregularity, recurrent diarrhea, and obstinate eczematoid conditions. Kneedler<sup>10</sup> emphasizes the possibility of atypical clinical manifestations, especially in malaria due to *P. falciparum*. The Surgeon General of the Army<sup>11</sup> advises succinctly that malaria should be suspected not only in patients with periodic chills and fevers but also in any obscure illness, febrile or non-febrile, in endemic regions. The symptoms of malaria may vary in different cases from mild headaches or diarrhea to severe chills and fever and to delirium or coma.

The severity of malaria in the puerperium is well appreciated. This has been explained on the basis that, during the delivery, a large amount of reticulo-endothelial tissue is lost with the placenta. Perez Acosta<sup>12</sup> calls attention to

malaria manifestations occurring even earlier on the basis of his experience with 113 *P. falciparum* and 30 *P. vivax* infected pregnant women admitted over a period of four years. Convulsions always indicate the necessity for blood examination, as does any febrile manifestation during the puerperium. Abortion and premature birth may easily be caused by malaria and malaria calls for prompt treatment, especially since malaria eclampsia is not rare.

### Diagnosis

The diagnosis of malaria must be based on the actual finding of parasites in the blood.<sup>11</sup> Blood is taken from the ear lobe or finger, preferably preceding, during, or immediately after a chill. The first and second drops are more likely to contain parasites than subsequent ones.<sup>13</sup> If parasites are not found, smears should be made on successive days. Wingfield's<sup>14</sup> experience emphasizes the unreliability of a negative result when obtained on the basis of a single blood film. On the first blood films of 60 patients *Plasmodia* were found in 42, on the second blood films 13, while the other five were detected by additional examinations. In *P. falciparum* infections there may be very few parasites in the circulating blood during the second 24 hours of each sexual cycle, since schizogony in this species takes place in the visceral circulation. In some latent cases the subcutaneous injection of 0.5 cc. of 1:1000 solution of **epinephrine** may result in finding parasites in the peripheral blood.<sup>11</sup>

The thin blood film, made in the same manner as that for a differential leukocyte count, is dried and stained with either Wright's or Giemsa's stain. Fever is believed to be produced by a parasitemia of one parasite in 100,000 red cells and it takes about one-half hour to ex-

amine that many erythrocytes in a thin film.

In thick blood films it is possible to examine between 15 to 50 times as much blood in a shorter period of time. Four small drops are placed on a slide within an area of 5 to 7 mm. and the blood is stirred with a pointed instrument into a square or circle measuring about 1 cm. for about one minute to defibrinate the blood.<sup>13</sup> After being thoroughly dried, simultaneous dehemoglobinization and staining are obtained by immersing the slide either in Wright's stain, diluted one part in 30 parts of distilled water for 30 minutes or, preferably, in Giemsa's stain, diluted one drop in 1 cc. of distilled water for 20 minutes.

Provided the thick blood films are not older than a few hours the rapid staining technic<sup>15</sup> may be used. Make a solution of Wright-Giemsa stains in proportion of one part of stain and nine parts neutral distilled water. Pour this over slides in a staining dish. Stain slides for ten minutes. Flush scum from top of the dish with neutral distilled water, then remove slides and wash them for one minute in neutral distilled water. Dry and examine with oil immersion.

**Preparation of Wright-Giemsa Stain<sup>15</sup>**—To make Wright-Giemsa stain, dissolve 2 Gm. Giemsa powder (National Aniline Chemical Co., Inc., N. Y.) in 100 cc. glycerine (C.P. from a freshly opened bottle). This may be done by heating in a water bath at 55 to 60° C. for two hours and mixing well at intervals with a glass stirring rod. To this mixture add 100 cc. Wright's stain solution (aged solution of 2 Gm. powder to 1000 cc. methyl alcohol). Let stand overnight and then add an additional 800 cc. of aged Wright's stain solution. Filter and use.

**Buffer Solutions**—To insure that the blue and red parts of the stain are taken

up in the correct degree by the parasites, buffered water of a pH of from 7.0 to 7.2 should be used for the dilution of the stock stains as well as for washing the stained slides. Disodium phosphate and either sodium or potassium acid phosphate in M/15 solutions are used. They are prepared by dissolving 9.5 Gm.  $\text{Na}_2\text{HPO}_4$  (anhydrous) per liter and 9.2 Gm.  $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$  per liter or 9.07 Gm.  $\text{KH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$  per liter. The two stock solutions are kept in separate glass-stoppered pyrex bottles from which are removed the following quantities to make the indicated amount of the buffered water.

pH	M/15 $\text{Na}_2\text{HPO}_4$	M/15 $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$ or M/15 $\text{KH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$	Dis- tilled water
7.0	61.1 cc.	38.9 cc.	900 cc.
7.2	72.0 cc.	28.0 cc.	900 cc.

The pH of the buffered water is tested and adjustments made as necessary.

**Serological Reactions — Precipitin Test**—Several authors have attempted to demonstrate precipitins in malaria immune serum. So far the results are rather inconsistent.

**Agglutination Test** — Agglutinins have been demonstrated in the sera of monkeys infected with *P. knowlesi* and birds infected with *P. gallinaceum*. Although agglutination occurs in high titers it is a species-specific reaction which requires living schizonts of the same species. The difficulty in obtaining such antigen makes this test impracticable for human malaria at the present time.

**Complement-Fixation** — Eaton and Coggeshall found antigen made of the monkey parasite *P. knowlesi* not only fixed complement in homologous monkey serum, but also in human malaria serum. The complement-fixation test was shown to be not species-specific, but group-



specific. Since complement was fixed in any malaria immune serum, this test became applicable for diagnostic purposes, especially since this antigen can be obtained in large amounts. Dulaney *et al.*<sup>16</sup> tested the sera of 317 persons. An amount of 0.1 cc. serum, 0.1 cc. *P. knowlesi* antigen, and two units of complement were used. Of 125 patients known to have malaria, 102 or 81.6 per cent fixed complement, while 23 reacted negatively. Of a total of 192 whose blood films were negative for malaria, 15 fixed complement, the others reacted negatively. Thus, in 88 per cent of the cases the complement-fixation test was confirmed. However, these workers obtained positive reactions in leprosy, amebic dysentery, and Chagas' disease. It appears that the complement-fixation test with *P. knowlesi* antigen may prove a useful diagnostic test.

#### **Wassermann Reaction in Malaria**

—An occasional positive Wassermann reaction in malaria has been known for quite a while. Harmsen and Hauer<sup>17</sup> examined the time element involved. These authors obtained 572 positive Wassermann reactions in 1000 malaria cases. The Wassermann reaction was positive when *Plasmodia* were in the blood, but occurred even in their absence. These authors state that a positive Wassermann reaction in the cerebrospinal fluid is never caused by malaria. While the reaction is usually negative in chronic cases and positive in acute cases, a positive reaction within three months after the attack of malaria is not considered proof for lues. They found a positive reaction even later than that, six months after the attack. Schwenkenbecher believes a positive Wassermann reaction to be the result of cell destruction with production of lipid substances, occurring in both lues and malaria.

#### **Treatment**

**Atabrine** is as efficacious as *quinine* for suppressive use as well as in the treatment of clinical cases.<sup>11</sup> Atabrine has been stated to cause mental symptoms. Actually,<sup>18</sup> the incidence of such untoward symptoms has been found small indeed. There is no report that atabrine, when taken "prophylactically," has ever produced mental symptoms. Attention is called to the fact that confusional psychoses sometimes occur as a direct result of malaria. Not every mental aberration is due to atabrine.

Covell<sup>19</sup> reminds us of the recommendations of the Malaria Commission of the Health Organization of the League of Nations (fourth report). Long continued administration of antimalarial drugs, when disease is latent, is not warranted. Short courses of treatment and moderate dosage are sufficient for primary attack and relapse. This will avoid undue interference in the acquisition of immunity.

While atabrine is equal in efficacy to quinine, it might be necessary occasionally to prescribe quinine when several courses of atabrine have failed to provide cure or the patient might not be able to tolerate atabrine. Quinine is difficult, if not impossible, to obtain at the present time. The U. S. Pharmacopeia has added in its twelfth edition **Totaquine**, which is a mixture of alkaloids from the bark of *Cinchona succirubra* or other suitable species of *Cinchona*. It should contain not less than 7 per cent and not more than 12 per cent of anhydrous quinine and a total of not less than 70 per cent and not more than 80 per cent of the anhydrous crystallizable cinchona alkaloids (cinchonidine, cinchonine, quinidine, quinine). The average dose recommended is 0.648 Gm. (10 gr.), three times a day, for seven days.

**Suppressive Treatment**—The term prophylactic treatment has been discarded, since it has been established that no drug will prevent the infection, but only suppress the clinical manifestations.

**Atabrine** for suppressive treatment is given as follows<sup>11</sup>: One tablet of atabrine containing 0.1 Gm. ( $1\frac{1}{2}$  gr.) once daily at the evening meal six days a week. Or: One-half of one tablet containing 0.05 Gm. ( $\frac{3}{4}$  gr.) once daily at the evening meal six days a week and at the evening meal on the seventh day one tablet containing 0.1 Gm. ( $1\frac{1}{2}$  gr.)

**Quinine** for suppressive treatment is given as follows<sup>13</sup>: Quinine sulfate (oral) 0.33 Gm. (5 gr.) on retiring daily.

**Plasmochin** should not be used for suppressive treatment.<sup>11</sup>

**Treatment of Clinical Attacks—Uncomplicated Malaria — Atabrine hydrochloride** 0.2 Gm. (3 gr.) and sodium bicarbonate 1 Gm. (15 gr.) by mouth with 200 to 300 cc. water every six hours for five doses, followed by 0.1 Gm. ( $1\frac{1}{2}$  gr.) three times a day after meals for six days.<sup>11</sup>

Instead of atabrine, **quinine sulfate** may be given: 1 Gm. (15 gr.) by mouth three times a day after meals for two days, followed by 0.6 Gm. (10 gr.) three times a day after meals for five days.<sup>11</sup>

The average dose of **totaquine** recommended is 0.648 Gm. (10 gr.) three times a day after meals for five days.<sup>20</sup>

The use of **plasmochin** in the treatment of malaria is not of value.

**Severe Malaria, or Malaria Complicated by Vomiting, Coma, or Other Serious Disorders:—Atabrine dihydrochloride**, 0.2 Gm. (3 gr.) in 5 cc. sterile distilled water injected *intramuscularly* with the usual precautions, into each buttock (total 0.4 Gm. [6 gr.]) If necessary, one or two additional doses of 0.2 Gm. (3 gr.) may be given

*intramuscularly* at intervals of six to eight hours. As soon as the patient can take and retain oral medication, **atabrine** is given by mouth in such doses as to give a total by both routes together of 1.0 Gm. (15 gr.) in 48 hours, followed by 0.1 Gm. ( $1\frac{1}{2}$  gr.) three times a day after meals for five days (total 2.8 Gm. in seven days).<sup>11</sup>

Instead of atabrine, **quinine dihydrochloride** 0.648 Gm. (10 gr.) in sterile physiological saline 300 to 400 cc. (minimum 200 cc.) may be injected *intravenously* with the usual precautions, especially avoiding speed. This treatment may be repeated in six to eight hours, if necessary. When the patient can take and retain oral medication, give a complete course with atabrine by mouth or quinine by mouth.

**Treatment of Relapses**—No drug known will prevent relapses with certainty. Treatment is not recommended for patients who are free of symptoms or those in whose blood parasites are not found. The treatment of relapses should be the same as that of first attacks.<sup>11</sup>

## AMEBIASIS

Amebiasis is caused by *Endamoeba histolytica* which lives in its active trophozoite stage in the mucosa of the cecum or more rarely the liver or other organs. When passed in feces the amebas are discharged either in the trophozoite or cyst stage, depending on the consistency of the stool. Formed feces contain the cystic stage only.

Transmission to other individuals takes place through fecal contamination. Feces containing trophozoites are not likely to transmit amebiasis, because they disintegrate soon after being discharged and should they be ingested, are destroyed by the stomach's acidity. The

more resistant cystic stage is responsible for the spread of amebiasis. Polluted water supplies may, under exceptional conditions, be the source of epidemics. Swimming pools may conceivably be suitable for infection. Human feces containing cysts, when used for the fertilization of truck gardens, may be a direct source. The infection may be carried to the consumer by sprinkling fresh produce in grocery stores with contaminated water. Food handlers have been incriminated and the thorough examination of food handlers and active measures for the control of dissemination of infection by them has resulted in a reduction of the incidence rate of amebiasis. Filth flies constitute a potential mechanism for the transmission of amebiasis, should they have access to human feces.<sup>21</sup> Since no animals of epidemiological importance are known to be infected, it would appear that proper fecal disposal is an efficient method of control. However, it has not sufficed to reduce the incidence in the United States. It seems that personal hygiene plays a much larger part than has been assumed. Ivanhoe<sup>22</sup> has studied the transmission of *E. histolytica* in a children's institution in which a high incidence had been maintained over a number of years, although the home was apparently clean and well kept. This author recovered *E. histolytica* cysts from the hands and soiled underwear of children, from damp sand in a play box, from the contents of a wading pool, and the concrete floor of the pool after draining. She concluded that direct contact transfer of *E. histolytica* in addition to pollution of the environment are major methods of transmission. Personal hygiene would help to reduce the incidence of amebiasis and at the same time of oxyuriasis, the epidemiology of which is similar.

## Symptomatology

Amebic dysentery presents a dramatic clinical picture and is well known, but nondysenteric amebiasis is much more widespread. Its recognition and treatment are of importance since these patients may develop dysentery at any time and in addition constitute a potential source of infection to the community. D'Antoni<sup>23</sup> has classified amebiasis on the basis of the number and location of the amebic lesions.

### I. Asymptomatic Amebiasis.

The lesions are small in number and not confined to a specific area. The patient is not cognizant of symptoms, since their onset is so gradual. Although asymptomatic, the patient is not a "healthy carrier." *E. histolytica* is an obligatory tissue parasite.

### II. Symptomatic Amebiasis.

#### A. Asyndromic (formes frustes).

The amebic lesions are not confined to a specific area. A mild toxemia is present and vague gastrointestinal disorders occur, including constipation and/or diarrhea, underweight, anorexia, vague or colicky abdominal pains.

#### B. Syndromic.

The lesions are usually confined to the ileocecal region. The symptoms simulate chronic appendicitis, peptic ulcer, or chronic cholecystitis.

#### C. Dysentery (acute or chronic).

The lesions are found throughout the colon, but especially in the rectum and sigmoid. The symptomatology is characterized by a true dysentery with tenderness and a bloody, mucoid discharge.

#### D. Hepatitis and Liver Abscess.

The lesions are in the liver tissue. The manifestations include fever, pain, and tenderness in the liver area, and a leukocytosis. It should be emphasized that stool examination does not necessarily reveal the ameba. Berne<sup>24</sup> classifies amebic liver abscess according to its location.

1. Acute costal type with the clinical manifestations of a chole-

cystitis or a penetrating or perforated duodenal ulcer.

2. Chronic costal type with the clinical manifestations of a carcinoma of the liver, stomach, gall-bladder, or colon, amyloid disease, pancreatic cyst, or hydatid tumor.
3. Acute pulmonary form with the signs of a basal pneumonia, empyema.
4. Chronic pulmonary form with the signs of a cancer of the lower lobe.  
Involvement of the left lobe of the liver will result in symptoms and signs in the epigastrium.

#### E. Involvement of Other Organs.

Abscess of lung, brain, skin, including the penis.<sup>25</sup>

The occurrence of amebomas (Ochsner) has been known for a long time. Several additional cases have been reported from the transverse colon, and the rectal ampulla by Cameron and Collins<sup>26</sup> and Niño<sup>27</sup>.

### Diagnosis

**Serological Reactions**<sup>28</sup>—Serological reactions for the diagnosis of amebiasis are feasible, but not practicable for clinical application at the present time. A skin sensitization has not been demonstrated. It is not known whether agglutinins occur, since natural flocculation and clumping occur. Wagener and Spector have examined sera for the presence of precipitins but the results were not conclusive and certainly not encouraging for diagnostic purposes. Complement-fixing antibodies in the sera of infected individuals have been demonstrated by Craig and, in his hands, the test has given reliable results.<sup>29</sup> Of 1,000 sera tested, 175 reacted positively and the results were confirmed by the recovery of *E. histolytica* from the stools of 157 or 90 per cent of the patients. A total of 825 sera reacted negatively and *E. histolytica* were detected in 12 or 1.4 per cent of these individuals. Thus the

positive reaction was 90 per cent and the negative more than 98 per cent reliable. This high specificity of the complement-fixation test for amebiasis, however, has not been confirmed by others. Magath and Meleny summarized their own work and that of previous workers and the specificity ranged from 21 per cent to 98 per cent according to the investigator. "The average for all cases so far reported is less than 70 per cent, a degree of sensitivity which would be totally unacceptable for complement-fixation in cases of syphilis."

The difficulty with serologic tests in amebiasis lies in the preparation of an antigen of consistent potency and stability. This difficulty is due to the fact that *E. histolytica* has not been cultivated in sufficiently large numbers in pure cultures. Cultures of *E. histolytica* can be maintained only in the presence of living bacteria. Craig, commenting on the complement-fixation test, states that it is inferior as a diagnostic test to the microscopic examination and should not replace such examination. It remains, however, a desirable test, since stool examinations are not always sufficient to detect the organism. This is especially true in patients with amebic liver abscess. Ochsner and DeBailey found the stools negative in 63.9 per cent of 131 such patients. Moreover, this test would facilitate the sometimes difficult differential diagnosis between *E. histolytica* and nonpathogenic ameba.

**Microscopic Examination**<sup>28</sup>—There remain for a specific diagnosis the actual recovery and identification of the causative organism from its environment, the intestinal contents. The material for examination is either the normally passed stool, a stool passed after a purgative has been given, or material obtained from rectal or sigmoid lesions by means of sigmoidoscopy. This material is ex-

amined either by one of the direct fecal technics (the unstained, the iodine stained, and the hematoxylin stained film technics); or by concentration technics (centrifugation and zinc sulfate centrifugal-flotation); or by enrichment technics (culture); or by a combination of these technics. Each type of specimen to be examined as well as each of the technics to be employed has advantages and disadvantages; none provides a means to detect all infections.

Fecal specimens become unsuitable for examination in the presence of oil or in an oily suspension, or if bismuth or barium have been taken previously. A purgative, if given, should be a saline cathartic, either *magnesium sulfate*, *sodium sulfate*, or a combination of *sodium phosphate and sodium biphosphate*. The second or third stool should be examined. Dysenteric stools grossly contain mucus and blood. Microscopically they show clumped erythrocytes in amebic and single erythrocytes in bacillary dysentery. Charcot-Leyden crystals may be found in amebic but not in bacillary dysentery. Large mononuclear cells, the macrophages, occur more often in bacillary dysentery and simulate amebic trophozoites.

While the examination of dysenteric exudates may suggest the diagnosis, the identification of the etiologic organism itself from feces is necessary.

Liquid or semiliquid specimens contain only the trophozoite stage of the ameba, formed stools only the cystic stage, while semifformed stools may contain both. Trophozoites are diagnosed either in an unstained suspension of physiologic saline or in hematoxylin stained films. Specimens suspected of containing trophozoites have to be examined within one hour after passage, as trophozoites of *E. histolytica* do not

encyst outside the human host, but disintegrate rapidly.

**Preparation of an Unstained Direct Fecal Film**—By means of a wooden applicator a representative fleck of the fecal sample is mixed with a few drops of physiologic saline on a slide. From a dysenteric stool the mucus and blood portion is preferred. A cover-glass is placed over the preparation and examined with low and high dry objectives. In such preparations amebic cysts appear as translucent discs, but no species diagnosis is possible since the internal structure of the organism cannot be seen. The diagnosis of the trophozoites of *E. histolytica* is based on the motility of the organism. The nucleus is not visible and only the demonstration of active motion by means of explosively protruded, clear pseudopodia evidences *E. histolytica*. Erythrocytes may sometimes be present within the ameba. Macrophages, as well as the trophozoites of nonpathogenic ameba look similar, but none move in the *E. histolytica* fashion. Without seeing clear pseudopodia rapidly thrown out, the diagnosis cannot be made in unstained direct fecal films. In these cases, hematoxylin stained films supplement the examination.

**Preparation of the Hematoxylin Stained Film**—Although there are quite a number of good modifications of the hematoxylin staining method, Faust's technic<sup>30</sup> is the least time-consuming. Trophozoites as well as cysts of the protozoa can be diagnosed in these films. The diagnosis of trophozoites of *E. histolytica* is based primarily on the morphology of the nuclear structure. The inside of the thin nuclear wall is lined with dark-stained, regular, minute chromatin beads. The karyosome is a dark-stained minute body in the center of the nucleus. The cytoplasm is finely granular with no vacuoles and the pseu-

dopodia, when present, are transparent. When the trophozoites die before they are fixed, vacuoles may show as a product of decomposition. Erythrocytes are sometimes present within the cytoplasm.

The rounded-up form of the trophozoites is still specifically diagnosable on the basis of the nuclear structure. The cystic stage is characterized by the presence of a thin cyst wall and one to four nuclei, rarely more. The specific diagnosis relies on the nuclear structure. In some cases, chromatoidal bodies are present, which, with hematoxylin, stain dark. If present, the shape of these bodies is specific for *E. histolytica*. They are sausage or grape shaped.

**Concentration Technics**—The direct fecal technics are the only methods for the diagnosis of trophozoites. All known concentration technics destroy the fragile, motile forms. Various concentration technics, however, facilitate the recovery of cysts. Removal of the fecal material and concentration of the cystic stages into smaller volume can be achieved by mixing the fecal specimen in a large quantity of water and allowing the cysts to settle to the bottom of the container. While the examination of the sediment provides a field fairly free from water-soluble substances this technic is time-consuming and its concentration efficiency is rather low. By means of centrifugation the time of sedimentation is shortened but the amount of water used in the centrifuge tubes to wash out the water-soluble substances is smaller. The examination of the sediment after repeated washings by centrifugation provides a microscopic field free from water-soluble substances and many of the bacteria, but the concentration efficiency of this technic is only a little above the diagnostic efficiency of the direct film. Flotation technics use a liquid medium of a specific gravity which is higher than

that of the objects to be recovered. The flotation principle was first introduced by Bass for the concentration of hookworm eggs from feces. Saturated sodium chloride solution was used. This solution, however, destroys cysts on account of its high osmotic pressure and ease of penetration through the cyst wall. Sugar solutions have been used by some workers, but the cysts are distorted, the viscosity of the suspension slows the levitation, and sugar is not a convenient medium. To utilize the flotation principle for protozoan cysts, zinc sulfate solution of a specific gravity of 1.150 to 1.180 is employed. Zinc sulfate permeates the cyst wall only after hours of contact.

**Preparation of a Concentrate by Zinc Sulfate Centrifugal Flotation**—The fecal specimen is comminuted in tap water in an approximate 1 to 20 proportion. It is preferable to remove large particles, such as undigested vegetable matter and others, by straining the suspension through one layer of wet cheese cloth in a funnel into a 100 x 13 mm. Wassermann tube. The preparation is centrifuged for about one minute at top speed in an International Clinical Centrifuge (2600 R.P.M., distance from axis to bottom of tube 13.5 cm.). The supernatant fluid is decanted, tap water added and the sediment broken up by shaking or by means of a wooden applicator. Washing by centrifugation is repeated until the supernatant fluid is clear. This usually takes three or four washings, depending on the type and amount of stool. At the final washing the sediment should just fill the bottom cavity of the tube. Where too much fecal material is present, the sediment is again broken up in water, the unnecessary portion poured off, and the preparation recentrifuged. The supernatant fluid is decanted, zinc sulfate solution of the specific gravity of 1.180 is added, the sedi-

ment broken up, and the preparation again centrifuged. Protozoan cysts have a specific gravity of about 1.050 to 1.100 and thus will rise. Fecal debris, although of a specific gravity of about 1.060 will settle to the bottom as it is porous (broken-up) material and is easily permeated by the zinc sulfate solution. This separation of parasites from fecal material provides a very satisfactory concentration, not only of protozoan cysts but also of eggs of helminths. The parasites are best removed from the surface film of the tube to a slide by means of a wire loop. Iodine stain is added to one or more loopfuls and thoroughly mixed. The iodine stain is either freshly prepared Lugol's solution or the stable D'Antoni's solution. No trophozoites of *E. histolytica* can be expected in such preparations; only cysts will be found. The differentiation of iodine-stained cysts of *E. histolytica* from those of non-pathogenic protozoa is based on the presence of a thin cyst wall, the number of nuclei (one to four), and the central position of the karyosome which does not stain with iodine and thus appears as a transparent dot. Diffuse brown-stained glycogen may be seen but occurs in non-pathogenic cysts as well. Chromatoidal bodies do not stain with iodine.

**Enrichment by Culture**—*E. histolytica* may be enriched by culture from freshly passed liquid or formed stool specimens. Culture tubes are inoculated with about 0.5 cc. of feces and incubated for 24 to 48 hours. One-tenth or more of 1 cc. of the sediment is pipetted off onto a slide for examination. The culture medium consists of Locke-egg-serum or Locke-serum or Tsuchiya's medium.<sup>31</sup>

**Evaluation of the Types of Fecal Specimens** — The normally passed formed stools show the encysted stage of *E. histolytica*. As a rule, the number of cysts is small in proportion to the

amount of feces. Thus several direct fecal examinations have to be made or concentration methods used.

A stool passed after a saline cathartic contains trophozoites washed down from the intestinal wall from the ileocecal area to the rectum. Only direct fecal technics are of value. The efficiency of this material for the diagnosis of amebiasis has been determined by Andrews who by stool examination after a purgative detected 75 per cent of those found infected by six consecutive stool examinations. Since six stool examinations by the technics employed by Andrews discover about 65 per cent of those actually infected, one purgative stool examination is likely to detect about 45 to 50 per cent of the actual infections. The low percentage is due to the fact that no concentration technic is available for trophozoites. Nevertheless, the efficiency is higher than achieved by any other single technic. The disadvantage is that after purgation the protozoa disappear temporarily from the following stool specimens. Purgation cannot successfully be followed immediately by examination of normally passed stools. The parasites reappear after three to six days.

Sigmoidoscopy permits the visualization of the lesions in the sigmoid or rectum and is quite efficient in recovering ameba from these lesions. However, Clark found lesions in the sigmoid and rectum only in 70 to 75 per cent of 186 autopsy cases and Rogers in 36 per cent of 36 autopsy cases. Since these were patients who died of amebic dysentery or its complications, the percentage of involvement of the sigmoid and rectum in patients having latent or mild amebiasis is probably much lower. This is illustrated by Faust's figures, arrived at by the study of accident cases. The cecum-appendix area showed a much more extensive involvement than the



sigmoid-rectum area. Amebiasis is essentially a cecal disease. On this basis, Craig<sup>29</sup> estimated that in amebiasis lesions in the sigmoid-rectum area occur only in about 30 per cent of those infected. When sigmoidoscopic material only is examined the diagnosis of some 70 per cent of the actual infections is likely to be missed.

The examination of any of the types of specimens is likely to miss some of the diagnoses and a combination of several types of specimens is indicated. The examination of normally passed feces, followed by that passed after purgation, followed by that obtained by sigmoidoscopy is recommended. The efficiency of the method by which such specimens are examined is obviously of importance.

**Evaluation of Fecal Examination Technics**—The culture technic is of value in the diagnosis of amebiasis when freshly passed specimens can be inoculated into culture tubes shortly after having been passed. Within this limitation its diagnostic efficiency is slightly higher than that of the direct fecal examination or sedimentation<sup>31</sup> and occasionally an infection missed by other technics is diagnosed on the basis of a positive culture. However, in general, the culture technic is likely to fail to diagnose a number of infections detected by direct or concentration technics.

The unstained direct fecal film is of value in demonstrating *E. histolytica* infections in which a liquid stool is passed, either naturally or artificially. The preparation is not time-consuming and the type of motion of the trophozoites permits specific diagnosis. However, the preparation cannot be kept permanently and not all infections can be detected, for the amount of material examined is only about 0.001 cc. of feces.

The hematoxylin stained film is of value in studying the detailed morph-

ology and thus to differentiate *E. histolytica* from nonpathogenic protozoa in cases where the iodine stain failed to show sufficiently definite characteristics. Hematoxylin stained slides can be kept as records, but their preparation is rather time consuming. Moreover, not all infections can be detected as the amount of feces examined is only about 0.001 cc.

While only these technics permit the diagnosis of trophozoites, the zinc sulfate centrifugal flotation is of value in the concentration of protozoan cysts. The amount of feces examined is about 0.2 cc. and the preparation is not time-consuming. Permanent mounts, however, cannot be kept.

In Fig. 2 are computed the probabilities of demonstrating *E. histolytica* from feces when the hematoxylin stained fecal film, the iodine stained fecal film and centrifugation, the zinc sulfate centrifugal flotation, and combinations of these technics are used.

None of these technics or combinations of technics provides a means to detect all infections with *E. histolytica*. Repeated examinations will reveal additional cases. The cumulative probabilities of demonstrating infections with intestinal protozoa are graphically presented in Fig. 3.

The black columns represent the positives found by examination of a single specimen, the open rectangles the additional cases detected by successive examinations. The efficiency provided by a single examination is rather low. It suggests that protozoa are not evacuated in consistent numbers with each stool. Such a quantitative fluctuation has been demonstrated.<sup>33</sup> The protozoa are discharged in cycles and the periods between two high tides run between 4 and 14 days. Thus, the four to five examinations necessary for a reliable examina-

PROBABILITIES OF DEMONSTRATING  
E.HYSTOLYTICA INFECTIONS

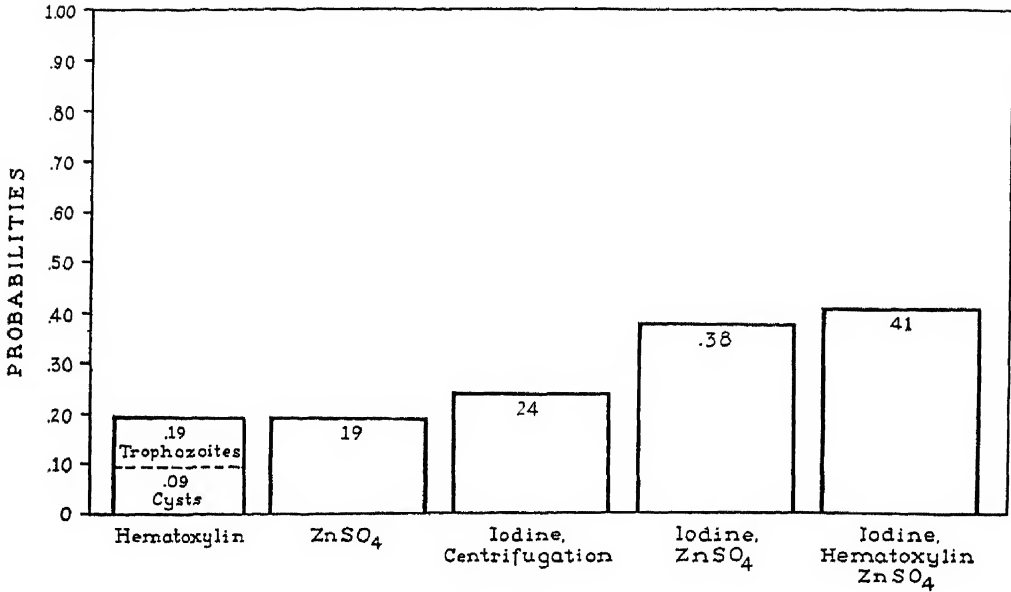


Fig. 2.  
(W. G. Sawitz: Clinics)

CUMULATIVE PROBABILITIES  
OF DEMONSTRATING INFECTIONS WITH INTESTINAL PROTOZOA  
BY MEANS OF  
A. UNSTAINED AND IODINE-STAINED FECAL FILM TECHNIC  
B. HEMATOXYLIN-STAINED FECAL FILM TECHNIC  
C. ZINC SULPHATE CENTRIFUGAL FLOATION TECHNIC

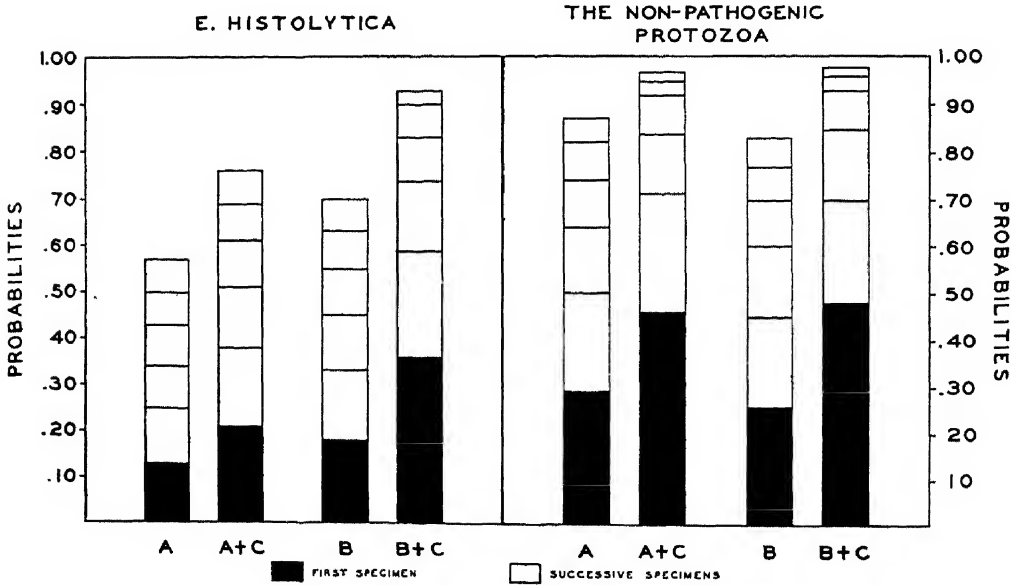


Fig. 3.  
(W. G. Sawitz: Clinics)

tion should cover a period of about 10 days, *i. e.*, be repeated every other day.

Nonpathogenic protozoa are much more easily detected than *E. histolytica*. The factors determining this difference are not well understood. Nonpathogenic protozoa are lumen parasites, and they are evacuated in large, although fluctuating numbers, since little, if any interference by the host takes place. Probably

examination. However, the examination cannot immediately be followed successfully by stool examination. On the other hand, the examination of three normally passed stools, followed by the examination of a purgation stool and eventually even followed by proctoscopy, is the procedure to be recommended. This procedure will detect more than 90 per cent of the positive cases.

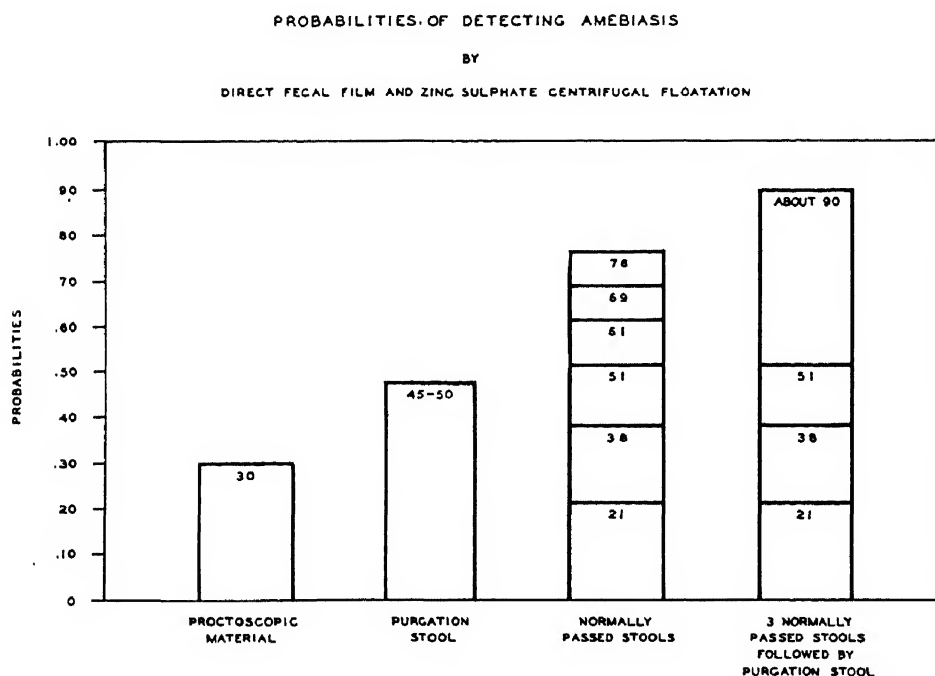


Fig. 4.

(W. G. Sawitz: Clinics)

one of the factors influencing the demonstrability of *E. histolytica* is that this pathogen is subject to the host tissue reaction and thus controlled in its reproductive rate.

Using these efficiency figures of technics, it is possible to plot the comparative values of the types of specimens to be examined for the diagnosis of amebiasis when a technic of known efficiency is employed. These values are presented in Fig. 4.

Proctoscopic material and purgation stools provide material yielding more positive results than any other single

Actually, in practice, we are not dealing with a group of positives and thus the term "percentage of positives" is misleading. The question from a practical point of view is, how reliable is a report of a positive result and how reliable is a negative report? A correct positive diagnosis depends wholly on the care and proficiency of the examiner. Assuming he is proficient, the reliability of a positive result equals certainty. The reliability of a negative result, however, depends on the true efficiency of the technic of examination employed and the prevalence rate of the infection.<sup>34</sup> Actu-

ally the prevalence of amebiasis in a particular group is not known, but we can assume that the prevalence rate runs approximately 10 per cent in the United States, higher in the South, lower in the North.

The reliability of a negative stool examination in the diagnosis of amebiasis when the prevalence rate is 10 per cent and when the direct fecal film and zinc sulfate flotation technics are employed is as follows: If proctoscopic material alone is examined, the negative result has a reliability of .93; if a purgation stool is examined .95; if one stool is examined .90; if two stools are examined .93; if three stools are examined .95; and if this examination is followed by proctoscopy .99.<sup>28</sup>

### Treatment<sup>23</sup>

It is generally recognized that patients with acute amebic dysentery or with amebic liver abscess should be treated. The necessity of treating asymptomatic patients is unfortunately not generally accepted, in spite of the fact that these patients may develop acute symptoms at any time. Moreover, they excrete the infective cystic stage of *E. histolytica* and spread the infection.

The treatment of patients with amebiasis has been recommended<sup>23</sup> as follows:

1. **Nondysenteric Amebiasis**—*Chiniofon* or *diodoquin*. If either of these drugs fail, *carbarsone* or *vioform* is indicated. If severe abdominal distress is encountered, *neoprontosil*.

2. **Amebic Dysentery (Acute or Chronic)**—*Neoprontosil* in conjunction with *chinofon* or *diodoquin*. If either of these drugs fail, *carbarsone* or *vioform* is indicated.

3. **Hepatitis, Liver Abscess, Involvement of Other Visceral Organs.** *Emetine* and treatment as for amebiasis.

**Surgical procedures** may be indicated in amebic liver abscess.

4. **Involvement of Skin**—*Carbarsone* applied locally as a 0.5 per cent solution may be successful.<sup>25</sup>

The dosages, methods of administration, efficacies, toxicities and contraindications of these drugs are listed below in alphabetic order.<sup>23</sup>

#### CARBARSONE

**Preparation**—Gelatin capsules each containing 0.25 Gm. (4 gr.).

**Dosage**—Adults: 0.25 Gm. (4 gr.) (1 capsule) twice daily for 10 days<sup>23</sup>; children: 0.0648 Gm. (1 gr.) daily per 20 pounds of body weight.

**Method of Administration**—Following the morning and evening meal, a 0.25 Gm. (4 gr.) capsule is given by mouth for 10 days. If *E. histolytica* is still present, the course may be repeated after a 10-day rest period. Daily routine including diet and exercise is not curtailed. Only severe cases require hospitalization.

**Efficacy**—Approximately 90 per cent.

**Toxicity**—Mildly toxic.

**Untoward Symptoms**—If toxic symptoms, abdominal distress, nausea, vomiting, exfoliative dermatitis<sup>35</sup> occur, medication should be stopped.

**Contraindications**—Liver and kidney disease.

*CHINIOFON (also marketed under the trade names of Anayodin and Yatren.)*

**Preparation**—Keratin-coated or uncoated pills each containing 0.25 Gm. (4 gr.).

**Dosage**—Adults: 1 Gm. (16 gr., 4 tablets) three times daily for seven days; children: 0.0648 Gm. (1 gr.) three times daily per 10 pounds of body weight.

**Method of Administration**—Following meals 1 Gm. (16 gr., 4 tablets) are given by mouth for a period of seven days. If no *E. histolytica* is found in the stools over a period up to six months, no further medication is necessary. If the stools remain positive, the treatment is repeated following a rest period of at least seven days. The drug may be administered without interfering with the patient's daily routine, and no precautions are necessary regarding diet or exercise except in those cases of amebiasis manifesting symptoms. Hospitalization is unnecessary except in severe cases.

**Efficacy**—Approximately 90 per cent.

*Toxicity*—Nontoxic in therapeutic doses.

*Untoward Symptoms*—In about 40 per cent of the individuals treated with this drug, a diarrhea appears on the second or third day, which lasts for one or two days and can be controlled by 8 cc. (2 dr.) *Tr. opii camphorata*, or *Kaomagma*, 12 to 18 cc. (3 to 6 dr.) following each defecation.

*Contraindications*—Essentially nil.

#### DIODOQUIN

*Preparation*—Tablets containing 0.21 Gm. (3.2 gr.).

*Dosage*—Adults: 1.5 to 2 Gm. (22.5 to 30 gr., 7 to 10 tablets) daily for a period of two to three weeks; children: 1 tablet daily per 15 pounds of body weight.

*Method of Administration*—The tablets are given following meals for a period of 20 days. The tablets may be chewed, an advantage in the treatment of children. If *E. histolytica* is still present, the course is repeated after a rest period of 7 to 10 days with the same or increased dosage. Daily routine including diet and exercise is not curtailed. Only severe cases require hospitalization.

*Efficacy*—Approximately 85 to 95 per cent.

*Toxicity*—Nontoxic in therapeutic doses.

*Untoward Symptoms*—None.

#### EMETINE

*Preparation*—Ampules containing 1 gr. of emetine hydrochloride in 1 cc. of solution.

*Dosage*—Adults: 0.068 Gm. (1 gr.) subcutaneously, not to exceed 0.778 Gm. (12 gr.) within a period of 40 days; children over 8 years of age: the dosage must not exceed 0.02 Gm. (1/3 gr.) daily.

*Method of Administration*—The patient is hospitalized and 0.03 Gm. (½ gr.) of the drug is given subcutaneously twice a day or 0.0648 (1 gr.) once a day on successive days for a period of 4 to 6 days.<sup>35</sup> No further injections are given for a period of one month, after which the course can be repeated.

*Efficacy*—Relieves symptoms in approximately 85 per cent of the cases; curative in only 33 per cent of cases. Relatively efficient in liver abscess. The only drug available.

*Toxicity*—May produce lowering of blood pressure, nausea, and vomiting. Extremely toxic if given in large doses or over a long period of time. Produces myocardial damage.

*Untoward Symptoms*—Toxic symptoms, such as sudden cardiac failure, myocarditis, wrist, ankle, or toe drop, muscular pains and weakness may appear during injections. Medication must then be stopped.

*Contraindications*—Myocardial, kidney, and liver damage. Children under eight years of age.

#### VIOFORM

*Preparations*—Gelatin capsules each containing 0.25 Gm. (4 gr.).

*Dosage*—Adults: 0.25 Gm. (4 gr., 1 capsule) three times a day for 7 to 10 days; children: 0.02 Gm. (1/3 gr.) three times a day per 15 pounds of body weight.

*Method of Administration*—One capsule is given by mouth after meals three times a day for 10 days. The course may be repeated following a rest period of seven days. Daily routine including diet and exercise is not curtailed. Only severe cases require hospitalization.

*Efficacy*—Approximately 80 per cent.

*Toxicity*—More toxic than Chiniofon, less toxic than Carbarsone.

*Untoward Symptoms*—In about 40 per cent of the individuals treated with this drug a diarrhea appears on the second or third day, which lasts for one or two days and can be controlled by 8 cc. (2 dr.) *Tr. opii camphorata*, or *Kaomagma* 12 to 18 cc. (3 to 6 dr.), following defecation.

*Contraindications*—Essentially nil.

If treatment is ineffective because of lesions in the lower colon or rectum, give *carbarsone* or *chiniofon* by rectum as follows:<sup>35</sup>

1. Carbarsone 2.0 Gm. (30 gr.) dissolved in 200 cc. of 2 per cent sodium bicarbonate solution. Give as retention enema at night, following a cleansing enema of 2 per cent sodium bicarbonate solution. Give on five consecutive nights, but if irritating reduce to alternate nights.

2. Or give chiniofon by rectum 4.0 grams (60 gr.) in 200 cc. of sterile water, after a cleansing enema of water.

*Vioform* and *diodoquin* are too insoluble and too irritating to be administered by rectum.

Following medication, pretreatment symptoms may persist for periods up to four months. The persistence of symptoms or their reappearance does not warrant treatment, however, unless the causative organism can be recovered from the patient. The post-treatment ex-

amination should include the examination of 12 to 15 stools over a period of six months.

## GIARDIASIS

*Giardia lamblia* is an intestinal flagellate which lives attached to the mucosa of the duodenum and jejunum. It is not considered to be pathogenic since it does not invade the mucosa. However, the constant irritation caused when present in large numbers may produce the clinical manifestations of a duodenitis. The organisms may cover the mucosa to such an extent that they interfere with the secretion and absorption. Ormiston, et al.,<sup>36</sup> called attention to the possibility of epidemic outbreaks of giardiasis with diarrhea. In the outbreak described children and adults were involved. Colicky pains, giddiness, weakness, anorexia, and headache accompanied the diarrhea.

The diagnosis is based on the recovery and identification of the organism. The examination of duodenal aspirate will reveal the trophozoite or active stage, while the examination of feces usually reveals the cystic stage.

**Treatment:** In 1937, Brumpt reported *acridine dyes* effective in experimental giardiasis and Galli-Valerio *atabrine* effective in human giardiasis. Since that time *atabrine* has been extensively used by a number of authors<sup>37</sup> with success in eradicating the infection.

**Dosage**<sup>38</sup> — Children, one to four years of age: One-half of one tablet containing 0.05 Gm. ( $\frac{3}{4}$  gr.) atabrine twice daily for five days.

Children four to eight years: One tablet containing 0.1 Gm. ( $1\frac{1}{2}$  gr.) twice daily for five days.

Children over eight years and Adults: One tablet containing 0.1 Gm. ( $1\frac{1}{2}$  gr.) three times daily for five days.

The tablets are given following meals, with increased water intake during the day. The tablets may be crushed and may be suspended in honey, syrup, etc. Atabrine treatment should not be repeated within 30 days.

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## NEUROLOGY AND PSYCHIATRY

### NEUROLOGY

BERNARD J. ALPERS, M.D., AND H. EDWARD YASKIN, M.D.

#### ENCEPHALITIS

At the end of the last war acute encephalitis was almost synonymous with encephalitis lethargica, which itself had been known for only a few years. Two years later the first cases of postvaccinal encephalitis were observed, and shortly thereafter it was recognized that smallpox, measles, and other exanthems were occasionally complicated by encephalitis with a pathologic picture of perivascular demyelination. Meanwhile, other epidemic forms of encephalitis, observed in different countries, were found to differ from encephalitis lethargica and from each other, and to be caused by neurotropic viruses differing from one another. Only a knowledge of etiology can bring order to the field of acute epidemic encephalitis, which at present is in a state of confusion.

**Recognition of Forms**—Considerable progress has been made in the recognition of various forms of encephalitis and their relationship to one another. For some time after the discovery of the St. Louis type, and the Eastern and Western types of equine encephalitis they were regarded as distinct forms, but Hammon<sup>1</sup> classes them together as "arthropod-borne virus encephalitis." Casals

and Webster<sup>2</sup> have been able to demonstrate a close relationship between the Russian tick-borne virus of spring-summer encephalitis of man and the tick-borne virus of the encephalitis of sheep known as louping ill in Scotland. *Culex tarsalis* mosquitoes were found to be hosts of both the Western equine and St. Louis viruses in Yakima. Since these findings several other mosquitoes have been demonstrated to be capable of transmitting the St. Louis infection in the laboratory. The rôle of mosquitoes as vectors of this disease now appears to be established. Epidemiologic evidence indicates that in the Yakima Valley, Washington, there is a widespread reservoir of these viruses. Strong evidence toward the incrimination of domestic animals, especially fowl, in this rôle is afforded by the results of neutralization tests on the sera of a large group of mammals and birds.<sup>3</sup> Vaccines against the equine viruses<sup>1</sup> and against the viruses of the St. Louis and Japanese B types<sup>4</sup> are now available, and should be used in selected groups of heavily exposed persons. Mosquito bite protection, larval control, arthropod vector control, and animal zoning restrictions in peripheral urban areas should afford protection in many epidemic areas.



**Infantile Western Equine Encephalitis**—Medovy<sup>5</sup> reports his observations of 17 cases of Western equine encephalitis seen in infants under one year of age. These cases occurred during the course of an outbreak of human equine encephalitis in Manitoba. The infants presented an almost identical clinical picture of fever, convulsions, bulging fontanel, generalized rigidity, increased globulin and pleocytosis in the spinal fluid. All but two were proven to be cases of Western equine encephalitis by complement fixation test. Treatment in each case consisted of *gavage feeding* and *general nursing care*. The administration of *maternal serum* or *sulfathiazole* did not ameliorate the clinical course. A number of the infants developed sequelae in the form of mental retardation and spasticity. Twelve cases made a complete recovery.

**Meningoencephalitis** — Sabin and Aring<sup>6</sup> report a case of meningoencephalitis in man caused by the virus of lymphogranuloma venereum. The syndrome presented by the patient was predominantly that of meningoencephalitis with a high temperature. Syphilis, tuberculosis, and lymphocytic choriomeningitis were at first considered in the differential diagnosis. Enlargement of the inguinal lymph nodes was present. The virus, identified by the type of pathogenicity in experimental animals and by cross immunity tests, was isolated on two occasions from the cerebrospinal fluid. The diagnosis cannot be made clinically but rests on: (1) The inoculation of spinal fluid into mice; (2) the complement fixation test made with the patient's serum and the specific antigen; (3) the Frei test, and (4) biopsy of a lymph node. Armstrong<sup>7</sup> recovered the virus of herpes simplex from the spinal

fluid of a suspected case of lymphocytic choriomeningitis.

A lymphocytic meningoencephalitis may occur in patients with pleurodynia.<sup>8</sup> An outbreak of 166 cases of pleurodynia occurred in Brooklyn in July, 1942. Howard and his colleagues call attention to symptoms previously not reported in these cases of pleurodynia. The most important points were the frequency of pharyngitis and the evidences of meningoencephalitis, which were noted in five adults. This was characterized by headache, apathy, vertigo, and photophobia. There was mild nuchal rigidity. The spinal fluid usually showed a lymphocytic pleocytosis. The patients recovered promptly and no sequelae were noted. The prominent symptoms in most cases were fever and severe pain in the upper part of the abdomen or the lower part of the thorax. This pain was sufficiently severe to embarrass breathing or to suggest some acute abdominal infection. Convulsions were common in infants.

**Toxoplasmic Encephalomyelitis** — The essential features of toxoplasmic encephalomyelitis were reviewed in last year's Service Volume. Koch and his associates<sup>9</sup> describe the ocular changes in six cases of infantile toxoplasmic encephalomyelitis. The essential lesion is a focal toxoplasmic chorioretinitis, bilateral and frequently multiple. The pathologic changes are necrotizing and inflammatory lesions in the retina and choroid similar to those found in the brain. Vail and his associates<sup>10</sup> report six cases of chorioretinitis of previously unknown etiology in which tests for the neutralization of antibodies for *Toxoplasma* were positive. They point out that many instances of chorioretinitis formerly diagnosed as tuberculous, metastatic, or of unknown etiology may be due to *Toxoplasma*, especially if cerebral calcification is present.

### Encephalitis Associated with Other Diseases

**Rubella**—An increase in the number of neurologic symptoms in the form of encephalitis and neuritis with rubella or German measles have been noted. The virus of rubella has been isolated from the spinal fluid of patients with meningo-encephalitis by Bradford.<sup>11</sup> Margolis and his associates<sup>12</sup> report 14 new cases of encephalomyelitis following German measles and summarize the clinical features of 34 cases previously reported. The course of the postrubella encephalomyelitis is characteristically short. Whether mild or severe, the duration of the illness is brief. Mild cases presented only such complaints as headache, vomiting, and stiff neck. The illness rapidly subsided. Fatal cases were remarkable for their severe, persistent convulsions, and for respiratory distress which was manifested by Cheyne-Stokes breathing or a slow respiratory rate and cyanosis. The first encephalomyelitic signs and symptoms appeared four days after the onset of the rash. Variations within the limits of one to six days occurred. In all patients an average interval of 3.9 days occurred between the onset of the rash and the first signs of encephalitis. The spinal fluid sugar determinations varied between 67 and 100 mg. per 100 cc. The protein was slightly increased, averaging 67 to 100 mg. per 100 cc. Spinal fluid cell counts varied from 8 to 500 cells, predominantly mononuclear.

**Scarlet Fever**—Because of the rarity of diffuse encephalomyelitis in the course of scarlet fever, Winkelman<sup>13</sup> reports such an occurrence in a young girl. The cerebral symptoms developed seven days after the onset of scarlatina. There was clinical evidence of widespread involvement of the entire brain stem and spinal cord. At necropsy, a type of perivenous encephalomyelitis resembling

that seen in measles, after vaccination, and the other known virus infections was observed.

**Measles**—Encephalitis associated with measles has been recognized as a clinicopathologic entity only for the last two decades. Litvak and his associates<sup>14</sup> report 56 cases with follow-up studies in 32 cases. They observed the following types of onset: (1) Sudden and abrupt, with convulsions, or with convulsions followed by coma and high temperature, in 50 per cent of cases; (2) gradual, with headache, listlessness, drowsiness, stupor, and coma, in about 40 per cent of the cases, and (3) gradual, with restlessness, delirium, irritability, confusion, and twitchings, in about 10 per cent of the cases. The time of onset of this type of encephalitis was more or less constant. The average period was four to six days after the appearance of the rash. The results of examination of the spinal fluid in these cases were not diagnostic of the disease. Fourteen of the 56 patients had normal spinal fluid findings. In all the patients the fluid was clear and usually under increased pressure. The sugar content was normal and in some cases slightly higher than normal. The protein content was usually increased. In one patient the spinal fluid showed an acellular hyperalbuminosis, a condition found in the Guillain-Barré syndrome (acute infectious polyneuritis). Follow-up study on 32 patients two months to seven years after discharge revealed that 22 had sequelae. Emotional instability, mental retardation, and extrapyramidal disorders were the most frequent sequelae in these cases.

**Postvaccinal Encephalitis** — This usually has its onset on an average of 10 to 12 days following inoculation with the vaccinia virus, although extremes of two to 35 days have been reported. Those

affected are as a rule in the age group from 4 to 16 years. Infants usually escape this complication. Reisman and Utz<sup>15</sup> report two cases with recovery. In both cases the spinal fluid was sterile, with a moderate lymphocytic pleocytosis, and showed an increase in protein. Dunn<sup>16</sup> reports a case of encephalomyelitis which occurred in an adult 15 days after vaccination. This patient made a complete recovery.

**Sydenham's Chorea** — Schwartzman and Grossman<sup>17</sup> review the results of treatment of 62 cases of Sydenham's chorea. *Vitamin B-6 (pyridoxine)*, *nirvanol*, and *typhoid-paratyphoid therapy* gave the best results in that respective order. Pyridoxine was given in doses of 23 mg. intravenously each day. Nirvanol was given in doses of 0.324 Gm. (5 gr.) twice a day and was discontinued if fever, drowsiness, or an eruption was noted. Frequent blood counts were done, and if the white blood count was 4000 or less, or if the eosinophiles were about 10 per cent, the drug was discontinued. In no case was it continued beyond 14 days. Typhoid-paratyphoid vaccine was given intravenously, starting with 0.1 cc. and increased by a small amount (usually 0.1 cc. [2 minims]) each day with the objective of producing a temperature as close to 104° F. as possible. Usually a course of ten injections was given. Uiberall and Uiberall<sup>18</sup> employed *blood transfusions* in the treatment of 22 patients with Sydenham's chorea. From 100 to 150 cc. was the average amount of transfused blood. The transfusions were given at intervals of three to four days. Generally, a total of three were given, but in stubborn cases as many as five were administered. Cure was obtained in 15 cases, great improvement in four, mild improvement in one, and no effect in two.

### Electroencephalography

The descriptive stage of clinical electroencephalography is now almost over and this branch of medical science is now entering its quantitative or interpretive stage. It is in this stage of development that electroencephalography will ultimately demonstrate its worth as a new diagnostic technic in neurology and psychiatry. Until standards based on a large number of uniformly classified cases are established, electroencephalographic diagnosis will be unreliable. The method is in use by neuropsychiatrists and neurosurgeons as an aid in the diagnosis of epilepsy and related disorders and as a painless and entirely safe method of detecting localized damage in the brain.

**Epilepsy**—Much emphasis is placed on epilepsy because that is the condition which presents the widest range of electroencephalographic abnormalities. The specificity of certain types of brain waves for epilepsy has come into question. In the course of obtaining 4500 electroencephalographic tracings of patients with a wide variety of neuropsychiatric disorders, Finley and Dynes<sup>19</sup> were impressed by the variation of abnormal patterns within any given clinical group and the similarity of many patterns in many diverse clinical disorders. An analysis of the tracings of 626 unselected epileptic patients revealed that 86 per cent of the tracings were borderline or abnormal and 14 per cent were normal. The spike and wave patterns usually furnished by epileptic patients occurred in less than 10 per cent. Less than half of these patterns were from patients with petit mal epilepsy. Because of these findings, the authors believe the use of clinical terminology in describing brain wave patterns of epileptic patients is misleading. Gibbs<sup>20</sup> found in an electroencephalographic study of 1000 normal persons and 1200 epileptics that.

although some supposedly normal persons show abnormalities of the type encountered in epileptics, certain disorders are so common in epileptics and so rare in normals that they have diagnostic value. Therefore, like a negative Wassermann reaction, a "negative" encephalogram is only suggestive. For that matter, a "positive" electroencephalogram is only suggestive. Low<sup>21</sup> emphasizes the importance of electroencephalography in the study of convulsive disorders in children. The importance of the electroencephalogram in determining the effect of anticonvulsive therapy is stressed by Goldman.<sup>22</sup> He found that with adequate, sustained treatment of the convulsive disorder, under electroencephalographic control, he was able to restore patients to freedom from seizures. According to Gibbs and her collaborators,<sup>23</sup> the problem of diagnosis and treatment of epilepsy often centers on the question of whether or not localizing signs are present. Electroencephalographic evidence of a focus of abnormal activity is an important localizing sign. A corroborating electroencephalographic focus was noted in 87 per cent of 106 cases with clinical localizing signs or symptoms. Clinical evidence of localized damage to the brain was 58 times as common in epileptic patients with electroencephalographic foci as in patients in whom the disturbance was generalized or absent. The same types of seizure discharge or other electroencephalographic abnormality were encountered in cases with focal electroencephalographic activity as in cases with nonfocal disorders. However, certain types of abnormality, notably irregular  $\frac{1}{2}$  to 3 per second activity spikes and 2 per second waves and spikes, were much more common in focal than in nonfocal records.

**Brain Trauma**—In brain trauma very evident disturbances of the electroen-

cephalogram are encountered. This fact has been utilized by physicians in the Armed Forces to study head injuries. Harris and his co-workers<sup>24</sup> found that in concussion with lack of neurologic evidence of brain damage, the electroencephalogram provides the neuropsychiatrist with a sensitive sign of cerebral damage. The significant change in the electroencephalogram after concussion seems to be the appearance of abnormal wave forms during hyperventilation of the patient. The use of the electroencephalogram as an index of cerebral damage from minor head injuries makes prognosis easier; thus much needed hospital beds may be released for other use by the military establishment. Schwab<sup>25</sup> found a normal record in most cases of mild head injury. In cases of severe injury an abnormal record persisted long after the clinical signs had cleared. Heppenstall and Hill<sup>26</sup> investigated 150 patients with posttraumatic syndromes. The electroencephalographic findings suggested that focal abnormalities in the tracings were associated with acquired cerebral trauma, and diffuse abnormalities with constitutional deficiencies. The presence of diffuse abnormalities in the electroencephalogram in posttraumatic states apparently does not of necessity indicate the presence of cerebral damage. According to Rosenbaum and Maltby,<sup>27</sup> the electroencephalograms of 65 per cent of 20 patients with eclampsia were indicative of cerebral dysrhythmia as compared with 2, or 10 per cent, of 20 patients with preëclampsia. Twelve of the patients with eclampsia had a family and personal history of convulsive disorders, while only two of the preëclampsia patients had a similar history. It is suggested that a primary cerebral dysrhythmia may be present in patients with eclampsia and that the associated toxemia may be the "trigger" mechan-

ism that exaggerates the inherent dysrhythmia to the degree that convulsions occur. A careful history with an electroencephalographic study might aid in predicting the development of eclampsia. Other conditions in which electroencephalography has been found to be clinically useful are as follows: Cerebral tumor, subdural hematoma, cerebral hemorrhage, cerebral thrombosis, cerebral abscess, encephalitis, behavior disorders, and psychopathic personalities.<sup>28</sup> It has almost no clinical value in schizophrenia, manic-depressive psychosis, feeble-mindedness, migraine, psychoneurosis, and hysteria.

The electroencephalogram has a definite place in the diagnostic armamentarium of the neuropsychiatrist and neurosurgeon. It must be evaluated in its proper position as a diagnostic tool. It is of practical value in the diagnosis and treatment of epilepsy if used as an adjunct to other laboratory data, the history, and the clinical signs and changes.

## EPILEPSY

**Anticonvulsants**—The use of *dilantin sodium* alone or in combination with *phenobarbital* in the control of convulsive disorders is now firmly established. However, these anticonvulsant drugs have not yet conquered the problem of cortical seizures and with neither is effective dosage always free from unpleasant toxic symptoms. The papers of Lennox,<sup>29, 30</sup> Peoples and Tatum,<sup>31</sup> McLendon,<sup>32</sup> and Macfarlane and co-workers<sup>33</sup> emphasize the above statements. Lennox states that the guiding principle in treatment consists of the increase of the dosage of dilantin by gradual steps until a maximum therapeutic result is achieved or, until symptoms of toxicity appear. Macfarlane and his colleagues say their experience verifies the neces-

sity of gradually replacing phenobarbital by dilantin and that the greatest benefit is sometimes obtained with synergistic use of both drugs. The electroencephalogram continues to be an important aid both in the diagnosis and in the control of treatment of epileptic disorders. Two years ago Cohen and Cobb showed that *azosulfamide* has a definite anti-convulsant action on some epileptics. These workers with Coombs and Talbot<sup>34</sup> have published the results of an intensive biochemical study on two of their patients, one suffering from grand mal and one from petit mal. While receiving azosulfamide in doses sufficient to reduce or stop their fits, these patients showed, under strictly controlled metabolic conditions, a decrease in CO<sub>2</sub> content and tension in the serum, some lowering of pH, and a positive potassium balance. It has long been known that a swing towards acidosis is likely to discourage attacks, especially those of the petit mal type. This type of fit is less amenable to phenobarbital and other anticonvulsants than are major fits, but is more amenable than major fits to starvation and the ketogenic diet, both of which produce acidosis. Waelsch and Putnam<sup>35</sup> have used *dl-Glutamic acid hydrochloride*, an acidosis-producing drug, in the treatment of petit mal and psychomotor seizures. This drug has been used in conjunction with known anticonvulsant therapy. Seizures associated with slow wave activity in the electroencephalogram, namely, those of the petit mal and psychomotor type, were decreased in frequency. Increased mental and physical alertness were noted during treatment. The number of cases studied is too small for final judgment, but further trial and observations are important.

**Prognosis and Age Incidence**—Nathrass<sup>36</sup> reports on the age incidence and prognosis in epilepsy based on a

study of 602 cases. Eighty-one patients developed seizures after the age of 40. Most of the patients continued to have epileptic attacks from time to time without other evidence of disease. Nathrass concludes that idiopathic epilepsy is by no means uncommon in persons of mature years. In the later years of life he found that epilepsy has remarkably little effect on intellectual powers and general health. It is interesting to note that seven patients in the older age group suffered from jacksonian seizures. Of this number, six died and at necropsy two were found to have cerebral arteriosclerosis, one had paresis, two had cardiac disease, and in one case no significant pathology could be found. Hence, he concludes jacksonian epilepsy gives no indication of the nature of the lesion.

**Diagnosis**—Garland and his co-workers<sup>37</sup> report on the water-pitressin test in the diagnosis of epilepsy. They feel such a test is valuable in the military services, where rapid recognition and disposal of epileptics is required. They believe the results of the electroencephalographic studies are not always conclusive; hyperventilation, small doses of metrazol, and the ethyl chloride spray test have on the whole proved unreliable. They investigated 196 cases. Of 44 with epilepsy, 17 (39 per cent) had a fit during the test. Of 32 with doubtful epilepsy, 12 (38 per cent) had a fit. Of 20 controls with hysterical personality, none had fits. Blyth<sup>38</sup> also reports favorably on the pitressin diagnostic test.

The régime of the test is as follows: The patient is kept in bed on a normal diet throughout the test and for 24 hours thereafter. A pint of water is given hourly from 7 A. M. until the test is discontinued, usually after 11 pints. Pitressin is given hourly from 10 A. M., the doses being 0.2, 0.3, 0.4, 0.5 cc., followed by four doses of 0.5 cc.—a total

of eight injections. The patient is weighed, after emptying his bladder at 6:55 A. M., at three-hour intervals for 12 hours, and again at the end of 24 hours. Fluid given includes water, lemonade, and milk. All fluid intake and output is measured. The test is stopped at once if a fit occurs, and 0.06 Gm. (1 gr.) of *phenobarbital* is given by mouth. It is also stopped if there is severe vomiting, abdominal discomfort, or severe headache.

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## NARCOLEPSY

Narcolepsy (diurnal episodes of unusual drowsiness or irresistible sleep) has been successfully treated with appropriate doses of *amphetamine sulfate (benzedrine)*. Eaton<sup>39</sup> has used *desoxyephedrine hydrochloride* in the treatment of 15 patients presenting typical symptoms of narcolepsy as the chief complaint. Of these, 10 patients gave histories of cataplexy in addition to somnolence. The drug was given in tablets of 2.5 mg. each and from two to eight tablets a day were prescribed. All but three patients expressed a preference for desoxyephedrine. No untoward reactions were noted.

Dynes<sup>40</sup> found that *potassium chloride* given in doses of 2 to 5 Gm. (30 to 75 gr.) daily by mouth succeeded in relieving all his patients with severe cataplexy of their disabling symptoms. He found that this therapy had no favorable influence on the somnolence.

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## MENINGITIS

**Meningococcic Meningitis** — The current increase in the number of cases of meningococcic meningitis in various parts of the country has emphasized recent advances in the treatment of the disease. These improvements depend almost wholly on the use of the *sulfon-*

*amide* compounds. *Sulfadiazine* seems to be the sulfonamide of choice at the present time for the treatment of the acute bacterial meningitides. Lumbar puncture is necessary practically only for initial diagnosis. The definitive status of the new antibacterial agent, *penicillin*, in the treatment of meningitis is not yet clear.

Beeson and Westerman<sup>41</sup> studied the results of sulfonamide therapy in cerebrospinal fever in 3575 cases which were submitted to the British Ministry of Health by more than 100 hospitals in England and Wales during the two-year period, June, 1939, to June, 1941. All but 19 patients were treated with sulfonamides, and 965 of them received some form of *specific serum therapy*. The disease occurred most often in infants and young children, 45.5 per cent of the patients being under 15 years of age. The host factor, particularly the age of the patient, is of distinct importance in determining the outcome of meningococcal infection, even with the aid of sulfonamide therapy. The fatality rates ranged from as low as 5.6 per cent in young adults to as high as 56.6 per cent in persons over 60 years of age. The fatality rate for all patients was 15.9 per cent; it was the greatest at the extremes of life and least in the 15- to 19-year age group. The most frequent complications were cranial nerve paralysis, arthritis, and deafness. There was no indication from the study that the administration of serum as an adjuvant to sulfonamide therapy was beneficial. In the treatment with sulfonamides a considerable variation seems to be possible in such matters as dosage, duration of therapy without noticeable effect on the fatality rate. Statistically, the results were about the same whether chemotherapy was begun early or comparatively late in the course of the disease. This

can be attributed to the fact that severe cases tend to be sent to the hospital sooner than mild cases. In the cases reported by Beeson and Westerman *sulfapyridine* was used almost to the exclusion of all other forms.

Jubb<sup>42</sup> reviewed 3206 cases of cerebrospinal meningitis surviving more than 24 hours after admission and treated in hospitals either by chemotherapy plus serum or by chemotherapy alone. In a series of cases treated from 1931 to 1934 with serum of improved quality and administered suitably, the death rate was 27.9, but a decrease of the rate for Great Britain did not occur until the introduction of chemotherapy. He notes that with the wider employment of the sulfonamide derivatives since 1938, the decline has been dramatic. In 1941 the rate was 19.5 per cent, and in the first half of 1942 it was 19.5 per cent as against 19.9 per cent in the corresponding periods of 1940 and 1941.

Military mobilization has been accompanied by serious outbreaks of cerebrospinal meningitis.<sup>43, 44</sup> Thomas<sup>45</sup> reports on the outbreak of meningococcal meningitis in the Fourth Service Command. He indicates that the amazing reduction in mortality from 39 per cent in the last war to less than 3.5 per cent in the present war is due entirely to chemotherapy. *Sulfadiazine* has proven to be the most satisfactory drug in the treatment of this condition. Patients with acute meningitis are controlled by an initial oral dose of 4 Gm. (60 gr.) of sulfadiazine followed every four hours by 1 or 1.5 Gm. (15 or 22.5 gr.) by mouth. The more severe form of meningitis may require an initial intravenous dose of 5 to 8 Gm. (75 to 120 gr.) of sodium sulfadiazine, depending on the patient's weight, to be followed by further intravenous therapy if the drug does not persist at an adequate level in the blood. Most impor-



tant is the prompt securing of a high blood concentration of 15 mg. per 100 cc. There is uniform agreement as to the need for immediate intravenous treatment with sulfadiazine and fluids (1000 cc. of 5 per cent dextrose solution).

Daniels and his colleagues<sup>46</sup> reported 80 cases of meningococcal meningitis. Seventy-eight of these patients were treated with *sulfadiazine*; the other two received *sulfapyridine* and recovered. Two patients who did not respond rapidly to *sulfadiazine* were given *polyvalent antimeningococcic serum* intravenously and recovered. In six of the sulfadiazine treated patients renal complications developed severe enough to make it necessary to substitute sulfanilamide for the sulfadiazine. One group received an initial intravenous "loading" dose of 0.1 Gm. (1.5 gr.) of *sodium sulfadiazine* per Kg. of body weight. A dose equaling one-half the initial dose was given parenterally every eight hours thereafter until the patient could retain the drug given by mouth. A concentration of 0.5 per cent or less of sodium sulfadiazine in isotonic solution of sodium chloride or sterile distilled water was used. Sulfadiazine was then administered by mouth, 1.0 to 2.0 Gm. (15 to 30 gr.) every four hours, until the temperature had been normal for from five to seven days. This dosage was adjusted when necessary in an attempt to maintain the blood concentration of sulfadiazine at 15 mg. per 100 cc. The fluid intake was maintained at 4000 cc. daily and the urinary output at 1200 cc. or more. The mortality rate in this series of 80 cases was 1.25 per cent. Hill and Lever<sup>47</sup> reported 68 cases with no mortality. Intravenous treatment with *sulfadiazine* as a routine was adopted for the first 24 hours. Kuhns<sup>48</sup> *et al.* used *sulfadiazine* in the prophylactic control of meningococcal meningitis. The

drug was administered prophylactically to more than 15,000 soldiers in residence at two posts where meningococcal meningitis was particularly prevalent during the spring of 1943. In one instance, 3 Gm. (45 gr.) of the drug were given by mouth daily for three days; in the other, the dose was 2 Gm. (30 gr.) daily for two days. Following the institution of prophylactic therapy the incidence of cerebrospinal fever among the treated individuals fell abruptly. Only two cases of the disease occurred during a subsequent period of eight weeks of observation. Meningococcus carrier surveys showed that the administration of sulfadiazine by mouth effectively lowered the carrier rate in the treated group at a time when the incidence of carriers among the untreated controls remained high or actually increased. Investigations have continued in a search for more therapeutically effective sulfonamides which at the same time provoke less toxic manifestations. It has been found that sulfadiazine<sup>49</sup> has a lower toxicity than its relatives. Nevertheless, it causes renal complications in a percentage of cases. For this reason, the therapeutic possibilities of the monomethyl derivative of sulfadiazine, *sulfamerazine*, have been investigated. Hall and Spink<sup>50</sup> report its administration to three patients suffering from meningococcic meningitis and two cases of meningitis due to type B influenza bacilli. All the cases recovered. Compared with sulfadiazine, when sulfamerazine was given orally, adequate blood concentrations necessitated smaller doses given less frequently. Sulfamerazine seemed to be tolerated quite well by small children and infants. No toxic reactions were encountered in 15 infants under one year of age. Lepper and his co-workers<sup>51</sup> gave sulfadiazine to 96 patients who had meningococcic meningitis, of whom 10 died, and sulfamerazine to

22 patients, of whom two died. They conclude that sulfamerazine is apparently as good a therapeutic agent as sulfadiazine. Geffer and his associates<sup>52</sup> used sulfamerazine for meningococcic meningitis during an epidemic of that disease in Philadelphia in 1942. The initial dose was always given intravenously as **sulfamerazine sodium** (5 per cent solution in sterile distilled water), adults receiving 3 Gm. (45 gr.) and children 1 to 2 Gm. (15 to 30 gr.). This dose was immediately followed by the oral administration of the drug, adults receiving 1 Gm. (15 gr.) every four hours and children receiving 0.25 to 1 Gm. (4 to 15 gr.) every six hours. Three deaths occurred in their series of 45 cases, a mortality of 6.7 per cent.

Blumberg and Gleich<sup>53</sup> outline the treatment of meningococcic meningitis in children. They point out that the therapy has two aspects: The intravenous administration of **5 per cent glucose in normal saline** offsets the dehydration and ketosis, while administration of **sulfonamide** has a bacteriostatic effect on the meningococci. The intravenous treatment is continued for 24 to 36 hours. The volume of infusion given varies from 2 to 4 Gm. (30 to 60 cc.) per pound of body weight per day, accompanied by oral fluid as tolerated. Sodium sulfadiazine, 0.06 to 0.1 Gm. (1 to 1½ gr.) per pound of body weight per day, is given intravenously. The initial dose is one-third to one-half of the total daily dose. This is followed by one-sixth of the total daily dose given every four hours. The same dose of sulfadiazine is given orally after the intravenous route is discontinued, until the patient's fever and abnormal signs and symptoms have been absent for a week. Urinalyses, blood counts, and blood sulfadiazine levels serve as guides in the course of the dis-

ease and therapy. One spinal tap is performed for diagnosis only.

Branham<sup>54</sup> finds **rabbit antimeningococcus serum** to be superior to the **horse serum**. Refined, concentrated rabbit serum is sometimes ten times as potent as the horse serum now in use. Antiserum is still of use in treating meningococcic meningitis, especially in patients who cannot tolerate sulfonamide compounds. Reimann<sup>55</sup> believes the polyvalent serum should be used, as it is difficult in some cases to determine the type of the causative meningococcus. Alexander<sup>56</sup> emphasizes the complementary nature of the action between the sulfonamide compounds and type specific antibody in their conquest of three types of meningeal infection (meningococcic, pneumococcic, and *H. influenzae* meningitis). She found that the greater the inhibitory influence of a sulfonamide compound, the greater the consequence of antibody formation by the host. The susceptibility of the meningococcus to the action of such a drug justifies the use of sulfadiazine alone in this type of meningitis, unless the patient fails to show a prompt response. Alexander believes that this antibody adjunct is necessary only for some of the infants and for patients of other age groups with overwhelming infections. The intravenous route alone is recommended for administration of antibody in all three varieties of meningitis.

**Pneumococcal Meningitis**—Recent reports on treatment of this condition still indicate that chemotherapy with or without specific pneumococcic serum is favored. The prevalent opinion is that **sulfapyridine** and **sulfadiazine** are equally effective. Hodes and his associates<sup>57</sup> reported their results in the treatment of 60 patients with pneumococcic meningitis. Of these, recovery occurred in 42 per cent after treatment

with the various sulfonamides. Sixty-four per cent of the patients over the age of two years recovered. This percentage is much higher than that obtained by others. Twenty-nine patients received specific serum in addition, but the authors were unable to conclude that those who received it were aided more than those treated by chemotherapy alone. They felt sulfadiazine was equally as effective as sulfapyridine, although they used the latter sulfonamide in most of their cases. Thomas and Twort<sup>58</sup> reported recovery of a case of pneumococcal meningitis treated with sulfapyridine and serum. In England, the sulfonamide known as **sulfamethazine** was successfully used by Pakenham-Walsh<sup>59</sup> to cure a case of pneumococcal meningitis. Alexander,<sup>56</sup> based on investigation of the biologic features of the organism, on experimental work on animals, and on results in the treatment of this infection in children, suggests that the ideal treatment combines specific antibody with sulfadiazine.

**Staphylococcal Meningitis**—MacNeal and his collaborators<sup>60</sup> were able to find records of only 48 acceptable examples of recovery from staphylococcal meningitis. During ten years of **bacteriophage therapy** of staphylococcal infections they record 11 recoveries from staphylococcal meningitis, of which seven were considered acceptable as recoveries from diffuse cerebrospinal staphylococcal leptomeningitis. They feel recovery from this form of meningitis may be achieved by use of bacteriophage without other therapy. However, they recommend the use of a **sulfonamide drug**, along with bacteriophage. Antitoxic serum may also be added to this therapeutic combination during the first week. Bacteriophage therapy should be continued long after apparent clinical recovery, in order to prevent sequelae, especially abscess of

the brain. The use of **penicillin** in this disease will be considered in another section.

**Streptococcal Meningitis**—Streptococcal meningitis prior to 1935 claimed a mortality of 95 to 97 per cent. Subsequently the literature began to see many reports of cases of streptococcal meningitis in which recovery occurred following the use of **specific chemotherapy**. Riley and Waugh<sup>61</sup> report a case of post-traumatic streptococcal meningitis treated successfully with **sulfadiazine**. **Penicillin** has been reported to be successful in effecting recovery in this type of meningitis.

**Influenzal Meningitis**—In *H. influenzae* meningitis most workers feel that a combination of **type specific antibody serum** and the **sulfonamides (sulfadiazine or sulfapyridine)** should be used. A number of British workers<sup>62, 63, 64</sup> have reported successful treatment of this type of meningitis with sulfapyridine in children. Moir<sup>65</sup> reviewed four cases of influenzal meningitis in which sulfapyridine was used. Two of the patients, one a child of 10 months, recovered. He states the concentration of the sulfapyridine in the cerebrospinal fluid should be as high as possible. Large doses of sulfapyridine should be given (never less than 3 Gm. [45 gr.] in 24 hours) and reduced doses should be given for at least a week after meningitic symptoms have disappeared. Dehydration and vomiting are best combated by **intravenous saline**, and this provides a convenient method for the administration of sulfapyridine which, he feels, is indicated in all cases of influenzal meningitis. Alexander<sup>56</sup> presents experimental and clinical evidence that a combination of **sulfadiazine** and **type specific antibody** is the treatment of choice. The following outline of treatment is suggested: When type B *H. influenzae* is established

as the infectious agent, a continuous infusion is set up. During the first four hours, in addition to sulfadiazine, a large quantity of fluid (40 cc. per Kg. of body weight) is introduced, in an attempt to speed up urinary excretion of specific soluble substance. This is advised on the premise that a given quantity of antibody is more effective if utilized mainly against carbohydrate in the capsules of the organisms. At the end of the first four hours large quantity of antibody is injected. The antibody, diluted in an amount of Ringer's solution or of physiologic saline solution, equivalent to 10 cc. per Kg. of body weight, is added to the reservoir of the continuous infusion. The administration of diluted antibody should be completed within two hours. The level of the spinal fluid sugar before treatment reflects the severity of the infection and is the basis upon which the dose of antibody to be given is calculated. The dosage of antibody recommended on this basis is:

Spinal Fluid Sugar (mg./100 cc.)	Mg. Antibody Nitrogen Indicated
Less than 15	100
15 to 25	75
25 to 40	50
Over 40	25

Twelve hours after the administration of the dose calculated, the temporary adequacy of treatment is tested by examining the patient's serum for its ability to produce capsular swelling of a suitable suspension of *H. influenzae*. When satisfactory excess of antibody is not demonstrable, an additional dose equivalent to 25 mg. of antibody nitrogen is given. If, at the end of 45 hours, evidence of satisfactory progress is lacking, a dose equivalent to 25 mg. of antibody nitrogen is given intrathecally. After sulfadiazine has been given parenterally for 24 hours and the patient seems better, 0.1 Gm. (1½ gr.) per Kg. is given daily

by mouth, and the dose is continued for seven days after the spinal fluid is first shown to be sterile.

**Friedlander's Bacillus Meningitis**—Meningitis caused by the Friedlander's bacillus is a medical rarity. The diagnosis is purely a bacteriologic one and rests on the finding of the organism in smears and cultures of the spinal fluid. Ransmeier and his co-workers<sup>66</sup> report a case and analyze 29 cases collected from the literature. They emphasize that in about one-fourth of these cases organisms were not found in the first smear. The spinal fluid is in no way characteristic, showing the usual changes of a purulent meningitis, with the cells in the exudate predominantly polymorphonuclear, an increased protein content, and a diminished sugar content. The disease occurs chiefly in infants and in adults, often after the fourth decade of life. In occasional cases confusion with meningococcic meningitis may occur because of the presence of petechiae and the lack of organisms in smears of the spinal fluid. Several patients with this type of meningitis have been reported cured with *sulfadiazine*.

**Otitic Meningitis**—To evaluate the results of treating otitic meningitis with the *sulfonamide* drugs, Williams and his co-workers<sup>67</sup> analyzed the 46 cases that they had observed during the five years before their advent and the 24 encountered since. Their results show that with *chemotherapy* and *drainage*, the recovery rate of adequately treated patients has been doubled during the past five years.

### Penicillin in the Acute Bacterial Meningitides

The antibacterial agent, penicillin, produced by the mold *Penicillium notatum*, was discovered by Fleming in 1929. Encouraging results are reported from use of this substance in the treatment of

infections. The substance as developed by British investigators is said to have several advantages over sulfonamide compounds. It is relatively nontoxic, nonhemolytic, and highly soluble, and its action is not inhibited by pus or by para-aminobenzoic acid. It is best given intravenously in physiologic solution of sodium chloride by the continuous drip method in doses of 30,000 to 40,000 Florey or Oxford units a day. Robinson<sup>68</sup> has tested the toxicity and efficacy of penicillin in certain bacterial, virus, and protozoan infections in mice. He found, on the basis of weight, that penicillin seemed more effective than the sulfonamides in streptococcal, pneumococcal, and staphylococcal infections in mice. Rammelkamp and Keefer<sup>69</sup> studied the effects of penicillin in certain types of pneumococcal and staphylococcal meningitis. Penicillin appeared in the blood stream for several hours after its intrathecal injection into patients with meningitis and its excretion was increased, suggesting that penicillin is absorbed more rapidly when the meninges are inflamed. No conclusion as to therapeutic efficacy could be reached on the basis of these cases. Florey and Florey<sup>70</sup> report a penicillin cure in one case of a sulfonamide-resistant streptococcal meningitis. They gave the drug by intramuscular injections; 15,000 Oxford units every three hours. They emphasize that penicillin can be given intravenously and intrathecally with little toxic effect. Pilcher and Meacham<sup>71</sup> reported on their treatment of experimental staphylococcal meningitis. They found that intrathecal injection with relatively small doses of penicillin greatly reduced the mortality rate (from 93 per cent in control experiments to 54 per cent in treated animals). Penicillin, when injected intrathecally, even in relatively large doses, produced a pleocytosis in the spinal fluid, but no

other significant toxic effect. The authors feel that intrathecal penicillin therapy will probably be valuable in treatment of clinical staphylococcal meningitis. Keefer and his co-workers<sup>72</sup> presented the results of treatment with penicillin in 500 cases of infection. The results in pneumococcal meningitis showed only seven recoveries among 23 patients (30 per cent). In two the meningitis was accompanied by endocarditis. In many of the 16 fatal cases the treatment was carried out with small doses given over a short period of time, and not all of them received penicillin intrathecally or intracisternally. A recovery occurred in a patient with a skull fracture complicated by streptococcal meningitis. Five patients with meningococcal meningitis were treated. One of these cases died. These workers conclude that the best results in the meningitides will be achieved by the intrathecal use of penicillin. Toxic effects were rare.

### Complicating Other Diseases

**Infectious Mononucleosis** — Uncomplicated infectious mononucleosis invariably has a benign outcome, and sequelae of any significance are rare. Sharf and Weir<sup>73</sup> report a case complicated by meningitis and review the literature. Of all the neurological manifestations encountered in this disease, involvement of the meninges is the commonest. Often the meningeal features antedate other evidences of the disease. Nuchal rigidity, positive Kernig's and Babinski's signs, convulsions, and mental changes have been present in some cases. Bilateral optic neuritis appeared in one case. The cerebrospinal fluid usually contains an increased protein and cellular content (chiefly lymphocytic), but examples have been reported in which the fluid had been normal in spite of clinical signs of meningeal irritation.

**Weil's Disease**—Clapper and Myers<sup>74</sup> report a series of cases of Weil's disease in which two presented clinical and laboratory evidence of meningitis. In seven cases there was an abnormal cellular reaction in the spinal fluid without clinical signs of meningeal irritation and in one meningismus was present without the spinal fluid showing pleocytosis. Polymorphonuclear cells predominate early and lymphocytes later. Cell counts on the spinal fluid reached 1000 or more per cu. mm. The dextrose content of the fluid was not altered. *Immunotransfusions*, they feel, may be of value in treatment.

**Meningitis Caused by the Higher Fungi**—The four higher fungi causing meningitis discussed by Skogland<sup>75</sup> are: *Actinomyces*, *Blastomyces*, *Torula*, *Coccidioides*. Man apparently acquires actinomycotic meningitis from contact with infected hay or grain. Infection almost always occurs following a primary infection elsewhere in the body, which spreads to the meninges by direct extension. The symptomatology of actinomycosis of the central nervous system varies with the form of the disease (meningitis, cerebral abscess, and cerebellar abscess). The prognosis is poor and all cases terminate fatally. Therapy is entirely symptomatic. Infection with *Blastomyces* is cutaneous, with primary involvement usually on the face or hands, and in a systemic form in which widespread dissemination of the organism occurs following invasion through the respiratory tract. The pathologic changes in the central nervous system are usually nonspecific and closely resemble those associated with tuberculous meningitis. There is no satisfactory therapy, and it is doubtful whether roentgen therapy, excision, and iodides have any beneficial effect after the meninges have been invaded. *Torula* meningitis is most com-

mon in men. The pathologic changes in the central nervous system are variable. There is no specific treatment. The fungus *Coccidioides* gains entrance through the lungs or the skin, and is subsequently carried by the blood stream to other organs. In about 25 per cent of patients the meninges are involved. The symptoms are nonspecific but are similar to those of other chronic meningitides, often with superimposed evidence of internal hydrocephalus. Coccidioidal meningitis is a fatal disease.

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### POLIOMYELITIS

**Pathology**—In no field of experimental neuropathology have advances been made more rapidly than in the case of poliomyelitis, and the successive additions to our knowledge within the past few years have necessarily involved the abandonment or modification of earlier views on such subjects as the portal of entry of the virus, the site and character of the essential lesion, and the basis of the characteristic clinical variants of the malady. The normal and usual method of travel of the virus throughout the body is reported<sup>76</sup> to be by the pathways provided by nerves. This is a neurotropic or neuronotropic virus. It leaves no demonstrable histologic change as it travels over or through the nerve fibers, yet its spread by way of neurons is dependent on healthy normal fibers. The rate of progression of the virus in peripheral nerves to the central nervous system has been calculated by Howe and Bodian to be at the rate of 2.4 mm. per hour in the experimental animal. Such travel has been found to occur in both the motor and the sensory fibers. Sabin<sup>77</sup> concludes that the portion of the central nervous system which is involved depends on the neural connections along which the virus spreads from the periph-

eral source. There is reason to believe that the virus invades from the alimentary tract through the fifth, seventh, ninth, and tenth cranial nerves to cause the bulbar form of poliomyelitis. To affect the lower extremities, the virus may traverse the afferent fibers from the intestine by way of the dorsal root ganglions. In the bulbar form of poliomyelitis there is a heavy concentration of neuronal lesions in the medulla, with fewer in the cord; in the spinal cord the reverse occurs. A crystalline protein fraction which may represent the virus of poliomyelitis, or at least a protein on which it is adsorbed, was obtained by Racker<sup>78</sup> from the brains of infected mice. In other experiments Bourdillon and Moore<sup>79</sup> obtained an apparently "pure" virus by ultracentrifugation. A group of Swedish workers<sup>80</sup> and Jungeblut and Bourdillon<sup>81</sup> have been able to secure electromicrograms of murine poliomyelitis virus, obtained either from infected mouse brains or from tissue culture preparations. The nature of the described structures at present must remain undetermined.

**Epidemiology** — Virus-infected rodents may be the source of outbreaks of human poliomyelitis according to a recent report of Jungeblut and Dalldorf.<sup>82</sup> These workers discovered a dead gray house mouse in the basement of the home of a fatal case of poliomyelitis. The viruses isolated from the dead house mouse and from the fatal human case were apparently identical in specificity and differed only in relative virulence. This is the first time that a probable extrahuman source of human poliomyelitis has been supported by experimental evidence. Faber's<sup>83</sup> recent demonstration of the hypersusceptibility of the oropharyngeal surface to virus of poliomyelitis adds to the concept of human poliomyelitis as a mouse-borne food in-

fection.<sup>84</sup> Maxcy and Howe<sup>85</sup> have reviewed the significance of the occasional in sewage of the virus. The demonstration of the virus in the stools of patients and of carriers has been supplemented by the findings of the virus in urban sewage in periods of maximal incidence of the disease. However, they conclude that the presence of the virus in sewage is without significance as far as the general spread of the disease is concerned. Present knowledge points to contact infection as the most important means of spreading poliomyelitis, the virus being present in the stools and secretions and in the walls of the pharynx of the patient. Trask and Paul<sup>86</sup> were able to detect the poliomyelitis virus in flies collected during epidemics of poliomyelitis. Toomey and his co-workers<sup>87, 88</sup> failed to recover the virus from sick dogs and cords from paralyzed chickens found in vicinities where human poliomyelitis had occurred. They likewise failed to isolate the poliomyelitis virus from urine of poliomyelitic patients with bladder paralysis.

**Prophylaxis and Treatment** — No certain preventive has been found. Brooks<sup>89</sup> recommends that children, especially those of the susceptible age, should keep physically fit with special attention to proper food, well supplemented by vitamins C, B, and D; rest, fresh air, and exercise, yet avoiding fatigue. Children of the susceptible immature type, especially those with poliomyelitic ancestry or those with positive Schick test, might be assured of more protection by adhering faithfully to a strict régime of this order. Harmon and Hoyne<sup>90</sup> report two cases of pregnancy complicated by acute anterior poliomyelitis. In the first case the death of the fetus occurred, presumably from asphyxia. They were unable to isolate the poliomyelitis virus from the fetal spinal



cord. In the second case a viable, non-paralyzed fetus was delivered. In the light of our present knowledge of the mode of spread of the virus of poliomyelitis, one may conclude that the failure of the disease to develop in the fetus of a mother with the disease is due to the low concentration of the virus in the blood stream or its absence. Hürney<sup>91</sup> reports the histories of two women who developed acute anterior poliomyelitis at the end of their pregnancy. All three children (one set of twins) were and remained healthy.

Stuck and Loiselle<sup>92</sup> report the clinical observations recorded during the 1942 poliomyelitis epidemic in San Antonio, Texas. Eighty-seven patients were treated by the *Kenny method* (reported in detail in the 1943 Service Volume) and a follow-up examination revealed more rapid recoveries than usual among those who were not severely paralyzed at the onset. From stool specimens of these patients a typical strain of the poliomyelitis virus was isolated. From flies collected in homes of some of these patients a strain of poliomyelitis virus was isolated.

Sister Kenny rationalized her treatment upon a new concept of infantile paralysis. According to this concept, three principal symptoms are found: "spasm," "mental alienation," and "incoordination." In view of this new concept Moldaver<sup>93</sup> conducted investigations which caused him to conclude that some of the concepts advanced by Sister Kenny are incorrect. Forty-nine patients with infantile paralysis were tested with chronaxia measurements and in some cases action potentials were recorded. He draws the following conclusions: (1) "Muscle spasm" is not "the most damaging symptom" and does not lead to neuromuscular degeneration. "Spasm" is not an entity but a complex phenomenon.

It is the result of a combination of the normal stretch reflex, meningeal irritation of the posterior roots, increase of the normal tonus in healthy and strong muscles or muscular fibers opposed to weak or paralyzed muscles, lesions of dorsal root ganglions and posterior horns. Pain is a common symptom in acute poliomyelitis. This is referred pain which is increased by stretching of the muscles. (2) In "alienated muscles" there is neither a functional paralysis nor a "physiologic block." That these muscles have partially or completely lost their power to contract is due to the fact that the anterior horn cells are damaged or destroyed. In the paralytic or paretic muscles considered to be "alienated," there is always some degree of neuromuscular degeneration. (3) "Incoördination" does not consist of a misdirection of nerve impulse. It is caused, if at all, by the inability of partially or totally denervated muscles to respond to otherwise normal nerve impulses. Watkins *et al.*<sup>94</sup> investigated the validity of the Kenny concepts of muscle dysfunction in poliomyelitis with electromyographic studies. Of the three concepts of Kenny, the only one upheld by their objective measurements is that of "incoördination," although the term, they feel, is misleading. Disordered reciprocal innervation seems to be a more descriptive term for this type of dysfunction. Although criticism of the Kenny concept of poliomyelitis is much in evidence, the acceptance of her therapy program during the acute stage of the disease is widespread.

Kabat and Knapp<sup>95</sup> have used *prostigmine*, orally, as an adjunct in the treatment of poliomyelitis. Their approach to therapy has been based on the Kenny concept of the disease. In a series of 20 patients, most of whom were in the subacute stage, the results were reported

as good. The drug increased the range of passive motion, decreased or eliminated deformities in some instances by relaxation of hypertonus, and in some cases improved active motion. The drug appeared to accelerate recovery. Stone<sup>96</sup> treated 11 patients with severe anterior poliomyelitis with *artificial fever* and *parenteral* and *oral vitamin therapy* during the acute stage. Four to ten fever treatments were given to each patient with a temperature range of 103° to 105° F. The fever was administered by means of an inductopyrexia cabinet. *Ascorbic acid* in doses of 150 to 200 mg. was given while the patient was in the cabinet together with fruit juices and saline solutions orally. Six patients received intramuscular or intravenous injections of *thiamin* (10 to 50 mg.) and *vitamins B* and *E* (12 to 24 cc. [3 to 6 fl. dr.] of vitamin B complex combined with 2 to 4 cc. [32 to 64 minims] of wheat germ oil). Good therapeutic results were reported by Stone in this series of cases. All the children have continued in good health.

### MENIERE'S SYNDROME

**Diagnosis**—Atkinson<sup>97</sup> suggests two important reasons for the failure of any particular treatment to achieve its hoped for results: (1) Laxity of diagnosis, and (2) the tendency to regard Ménière's syndrome (recurring vertigo, deafness, and tinnitus) as a disease *sui generis*. An accurate diagnosis demands a careful neurologic examination, Bárány tests, examination of patency of the eustachian tubes, and general examination to determine the presence or absence of any associated condition, and, when the diagnosis is still not made, idiopathic Ménière's disease must be considered. This large remaining group of cases can be divided into at least two divisions, each with a different cause. Some may have an al-

lergic basis and the others, almost four-fifths of the total, may be insensitive to histamine. In these cases the mechanism is primarily vasoconstrictor in contrast to vasodilator of those with an allergic basis. Classification, according to the etiologic basis, which is tentative, and expresses present knowledge, is as follows: (a) Lesions interfering with the function of the eighth cranial nerve because of (1) lesions of the cerebellopontine angle and (2) degenerative vascular disease. (b) Lesions interfering with the function of the labyrinth because of (1) alteration in intralabyrinthine pressure: (a) from without, stricture of the eustachian tube, and (b) from within, increased production of endolymph (primary vasodilatation, allergy, sensitivity to histamine; (2) vascular disease: (a) angiospasm; primary vasoconstriction and (b) arteriosclerosis; (3) toxic labyrinthitis, that is, focal infection.

Atkinson<sup>98</sup> concludes from a series of cases that the syndrome of Ménière and migraine are identical in the mechanism of their production, which is a vascular one. They differ in the location of the impact. The two syndromes differ, too, in the frequency of occurrence of the two groups. Whereas in Ménière's syndrome the primary vasodilator group is a relatively small one compared with the vasoconstrictor, in the migraine syndrome the position, if not reversed, is at least more equal. Allergy as a cause of migraine is common, as a cause of paroxysmal vertigo it is uncommon. In the group characterized by primary vasoconstriction, attacks were relieved for a period of several months with the use of nicotinic acid (25 to 50 mg.) daily.

**Treatment**—Rainey<sup>99</sup> reports on his results in the treatment of 22 patients with *histamine* intravenously. In 17 cases the results were excellent, and in five patients the effects were disappoint-

ing. The technic for treating these patients is as follows: 1 cc. (16 minims) of histamine phosphate (2.75 mg.) is diluted in 250 cc. (8½ fl. oz.) of isotonic solution of sodium chloride. This is given drop by drop at the rate of 70 drops to the minute. Some patients may tolerate only 40 to 50 drops a minute. Many patients complain at first of constriction of the chest, hence it is best not to give more than 20 to 30 drops a minute for the first five minutes. At first the face is flushed and within 15 to 20 minutes the erythema spreads over the body. The blood pressure is determined every 10 minutes. Rainey feels that one should give at least two intravenous treatments and in some cases three on alternating days.

Asenjo and Riesco<sup>100</sup> treated 18 patients with Ménière's syndrome by giving 6 to 8 Gm. (90 to 120 gr.) of *potassium chloride* daily, 0.25 Gm. (4 gr.) of *Vitamin B<sub>1</sub>*, *nicotinic acid*, and a *diet rich in vitamin B*. The treatment was continued for a period of four to six months. The immediate and late results were good in 12 patients who were observed for more than three years. *Resection of the acoustic nerve* was resorted to in three of the four cases in which medicinal therapy failed. The results were excellent.

Schick<sup>101</sup> treated 18 cases of Ménière's syndrome, of the idiopathic type, with intravenous injections of 5 cc. (80 minims) of 50 per cent magnesium sulfate solution two or three times weekly. From 10 to 20 doses were given depending upon the response and the severity of the condition. The injections were given very slowly. Seven cases remained free from attacks during a 14-month period.

### MIGRAINE

Atkinson<sup>98</sup> believes that vascular dysfunction is the underlying causative

mechanism which relates migraine and Ménière's syndrome. He separates migraine disorders into two groups according to the response to *histamine*. Patients who are sensitive to histamine manifest primary vasodilation and those who are not sensitive to histamine have primary vasospasm with secondary vasodilatation. He feels migraine is more prevalent in the vasodilator, histamine-sensitive, allergic group than in the spastic group.

**Treatment**—This is directed toward the underlying cause of vascular dysfunction. If it is allergic and the allergy cannot be found, histamine desensitization is helpful. In the primary vasoconstriction type of migraine, *niacin* is used to produce dilatation. Gottlieb<sup>102</sup> believes, after a study of a large group of patients, that *benzedrine sulfate* is an adequate substitute for *ergotamine tartrate* when the latter is ineffective or productive of toxic symptoms. To abort an acute attack benzedrine was given intravenously in 3 to 20 mg. doses. The rate of injection was 1 mg. per minute for the first injection. The speed of injection was controlled according to the rise in the blood pressure which was taken at minute intervals. Some patients were advised to take the drug orally in doses of 10 to 40 mg. at the beginning of an attack. It may be administered by mouth daily in repeated small doses as a means of preventing attacks.

Hines and Eaton,<sup>103</sup> and Engle and Evanson<sup>104</sup> reported on the use of *potassium thiocyanate* in the treatment of migraine. The first two workers found that if they could achieve a satisfactory blood thiocyanate level (6 to 12 mg.) in their patients, they could produce relief. In the majority the frequency of headache was reduced by 75 per cent. The latter two authors studied the effects of the drug in 13 patients suffering from

migraine. They concluded that potassium thiocyanate in daily oral doses sufficient to produce a blood concentration of 2.5 to 8 mg. per 100 cc. is effective in the treatment of this condition. Taken in 0.389 Gm. (6 gr.) doses during the preheadache phase it is useful in aborting the headache. It was of no value when taken after the onset of actual headache.

Brown<sup>105</sup> reports the use of *urea* in preventing attacks of migraine. Three patients were benefited by this treatment. His therapeutic régime is: 20 Gm. (5 drachms) of urea in water are given three times a day for a week; a similar dose two times a day for a week; subsequently 20 Gm. (5 drachms) in a single daily dose for an indefinite period. There were no untoward effects.

### MYASTHENIA GRAVIS

Interest continues to focus on the possible relationship between the thymus gland and myasthenia gravis. The findings of Blalock, Campbell, and others in this regard were reported in the 1943 Service Volume. McEachern<sup>106</sup> feels that the general character of myasthenia gravis suggests an endocrine disorder. He points out that roentgenologic evidence of thymic enlargement or tumor is rare in myasthenia gravis, although experience at necropsy leads to the anticipation of an abnormality of the organ in about half of the cases. He reports 13 patients with myasthenia gravis who had their thymus or thymic tumor removed and seemed improved; the improvement in a few amounted to cure. Complete disappearance of myasthenic symptoms did not result in all of the cases, despite apparently *complete thymectomy*. Sloan<sup>107</sup> examined 350 thymus glands removed at necropsy. The thymus glands of 10 patients with myasthenia gravis

were no larger than many apparently normal glands. The pathologic changes in the majority of these glands were in no wise different from the changes found in the thymus glands associated with other diseases.

Winton<sup>108</sup> emphasizes in his report that this condition may present itself with only a monocular symptom such as ptosis or diplopia secondary to a monocular muscle paresis. The importance of doing the prostigmine test in suspicious cases is stressed. Laurent and Walker<sup>109</sup> emphasize that *prostigmine* can be given over a great period of time effectively and enable patients to lead relatively useful and happy lives. They have used this drug successfully over a period of nine years in 18 patients. Dosage depends upon two main factors: the fluctuations of the disease, and the regularity of the patient's activity. For patients who lead an active life these authors allow a daily ration of 15 tablets (15 mg. each). The patient takes them to suit his requirements. *Atropine*, 0.00065 Gm. ( $\frac{1}{100}$  gr.), is also taken two or three times daily if and when required. All of their patients take some adjuvant drug — *quinidine*, *ephedrine*, or *potassium salts* — and these, they feel, reduce the amount of prostigmine needed. They stress adequate dosage in this disorder. Nielsen<sup>110</sup> reports the occurrence of bromidism after excessive dosage (240 mg. daily) of *prostigmine bromide* for myasthenia gravis. He feels this danger can be avoided by stringent supervision or by an occasional change to *prostigmine methylsulfate*.

Eaton<sup>111</sup> describes the use of *quinine* as a diagnostic test for myasthenia gravis. This test depends upon the weakening effect of quinine which heightens the myasthenic symptoms. It is less often necessary than the test with prostigmine

methysulfate, but is of equal value in particular cases such as (1) those in which demonstrable weakness is so slight that the response to prostigmine is not conclusive, and (2) those in whom the weakness is not demonstrable and the subjective response of the patient would have to be relied on. Three doses of *quinine sulfate*, 0.65 Gm. (10 gr.) each at two- to three-hour intervals, usually are given and the patient is observed for the appearance of any weakening effect.

### NEURITIS

**The Sciatic Syndrome**—There is no more difficult problem in the fields of neurology and orthopedic medicine than the diagnosis of the etiology of sciatic pain. There is the impression among many observers that a primary mononeuritis of the sciatic nerve is rare and that practically all the cases of sciatica are secondary in origin. Add to this the recent popularity of nucleus pulposus herniations as a cause of sciatica, and it becomes clear that the entire group of sciatica cases requires careful analysis, particularly with reference to associate means of differentiating cases of primary sciatic neuritis from those of secondary sciatica. The 55 cases analyzed by Alpers and his associates<sup>112</sup> were selected as authentic examples of primary sciatic neuritis. Thirty-seven, or 67 per cent, of the cases were in males, all but four of whom were engaged in heavy work and were exposed to changes in weather. Sciatic neuritis is a disease of middle age or early old age. It is characterized by tenderness of the nerve trunks and usually also of the muscles of the thigh and calf. The authors conclude that while cases of secondary sciatica outnumber the primary cases, true sciatic neuritis is not a rarity. The causes of sciatic neuritis are those of neuritis in

general and those cases for which no cause is found should not be regarded as idiopathic. It is surprising to read that many clinicians regard the diagnosis of a protruded intravertebral disk, on the sole basis of a sciatic syndrome, as a simple matter. Some clinicians have an utter disregard of spinal puncture and of contrast medium studies prior to operation for the majority of cases. This position seems untenable. Yaskin and Tornay,<sup>113</sup> based on their experience with 50 surgically treated cases of protruded disk and hypertrophied ligamentum flavum, emphasize that, in the final analysis, the diagnosis of a herniated disk as the cause of a sciatic syndrome, depends to a great extent on the exclusion of other conditions. Therefore, before arriving at the diagnosis of a prolapsed disk, especially before advising operation, the clinician should be mindful of and rule out the following conditions:

**Orthopedic Conditions**—Spinal anomalies, spondylolisthesis, sacroiliac disease, lumbosacral disease, inflammations and neoplasms of the vertebral column, disorders of the articular facets, infections of the soft tissues (myositis, fibrositis, fasciitis), spasm of the fascia lata and piriformis muscles.

**Primary Neurologic Conditions**—Neuritis, radiculitis, ganglionitis (including herpes zoster), lesions of the cauda equina and of the spinal cord, with special reference to specific infections and tumors.

**Visceral Disease**—Posterior peritoneal cavity and pelvis, especially the lower genitourinary tract, prostate, and rectum.

**Systemic Processes**—Focal infections, deficiency states.

**Psychalgia**—Hershey<sup>114</sup> demonstrated anatomically that pain of sciatic radiation could be caused by disease of

the sacroiliac joint. The lumbosacral trunk was in direct contact with the sacroiliac joint at the point at which it traverses the joint in its lower one-third in all of 64 cadaver specimens studied. Hypertrophic arthritis in the form of severe spur formation on the anterior line of the sacroiliac joint was found to be present in 25 per cent of the bodies that were studied. Most of these were considered capable of producing direct irritation of the lumbosacral trunk. Good<sup>115</sup> reports the diagnosis and treatment of sciatic pain in about 65 army men where, he feels, the etiology was myositis. Well-defined myalgic spots, harder than the surrounding muscle, could be found in the quadratus lumborum, glutei, or tensor fasciae latae muscles. Pressure on these produced agonizing pain. The distribution of the spots did not correspond with that of the pain complained of, which was a referred one. Injection of *procaine* into these spots removed both the local tenderness and the referred pain. Savitsky and Strauss<sup>116</sup> report two cases of subarachnoid hemorrhage where pain in the sciatic distribution was the presenting symptom.

**Cervical Radiculitis** — Semmes and Murphy<sup>117</sup> report a new syndrome due to the unilateral rupture of the sixth cervical intervertebral disk. The subjective symptoms simulate those of coronary disease and are due to compression of the seventh cervical nerve root. The syndrome is characterized by pain in the neck which radiates to the shoulder, precordium and arm, and by sensory changes in the index and middle fingers. They conclude that an undetermined number of patients who heretofore have been thought to have coronary occlusion, angina pectoris, hypertrophic arthritis of the cervical spine, neuritis of the brachial plexus, bursitis, scalenus anticus syndrome, or cervical rib have a rupture of

one of the lower cervical intervertebral disks.

**Guillain-Barré Syndrome** — Since Guillain, Barré, and Strohl described a peculiar form of polyneuritis coexisting with normal cell count and increased protein content of the spinal fluid, considerable attention has been devoted to the problem of differentiation between this type of polyneuritis and acute anterior poliomyelitis. It is mainly by the clinical manifestations, the laboratory observations, and the final outcome that a differentiation between the Guillain-Barré syndrome and poliomyelitis is usually made. Jervis and Strassburger<sup>118</sup> describe the case of a patient who showed the clinical manifestations and laboratory findings of an infectious polyneuritis and whose disease, after study of the spinal cord after necropsy, was determined to be acute anterior poliomyelitis. The hypothesis is advanced that a number of cases of the Guillain-Barré syndrome may actually be instances of anterior poliomyelitis with favorable outcome. Hence, one must attempt to isolate poliomyelitis virus or another virus from patients with "infectious polyneuritis." Sahs and Paul<sup>119</sup> differentiate neuronitis or acute infectious polyneuritis from poliomyelitis by the fact that the latter rarely progresses after the second week of illness, and its segmental or "spotty" distribution differs from the symmetric pattern of neuronitis. In contradistinction to neuronitis, systemic manifestations of poliomyelitis are rapidly followed by meningeal irritation and paralyses, but cranial nerves are infrequently affected; the spinal fluid shows only slight elevation of the total protein and pleocytosis is the outstanding diagnostic feature.

**Retrobulbar Neuritis** — Benedict<sup>120</sup> reviewed the records of more than 400 patients with retrobulbar neuritis. By

elimination of other factors which might cause blindness, multiple sclerosis was suspected in 90 of the 400 patients. In 41 of the 90 patients further evidence of multiple sclerosis has appeared.

**Peripheral Neuritis** — Dynes and Norcross<sup>121</sup> found that in a series of 92 cases of pernicious anemia, 21 or about 23 per cent demonstrated evidence of peripheral neuritis and combined system disease. An additional 24 per cent showed combined system disease without peripheral neuritis. They treat patients demonstrating neurologic complications with 20 U.S.P. units (3.3 U.S.P. units per cc.) of *liver extract* intramuscularly each day for several weeks and then continue this dose every second day for several months. Large doses of a potent *vitamin B complex* preparation are given in addition. Of 21 cases with neurologic complications, 16 have responded well. Needles<sup>122</sup> studied seven cases of diabetic neuritis before and after therapy with *thiamine chloride*. No improvement was noted. Saksena<sup>123</sup> reports paralysis of the serratus anterior muscle after glandular fever. It occurred on the fifth day of illness and was present one year after its onset. Hauser and Martin<sup>124</sup> report two cases of traumatic paralysis of the serratus anterior muscle following wearing of a full pack by soldiers. Treatment consisted of a supporting splint, heat, and massage to the shoulder. The paralysis of the musculospiral nerve which innervates this muscle causes the typical finding of winged scapula on the involved side. Joliffe<sup>125</sup> has observed that symptoms of polyneuritis which are identical to those of beriberi occur in association with various diseases. The disorders which cause such symptoms are those which increase the requirement, prevent the absorption, or impair the utilization of vitamin B<sub>1</sub>. Polyneuritis occurs in gastrointestinal

diseases, in alcoholism, in pregnancy, in infectious diseases, and in cachexia. The earliest signs are plantar dysesthesia and calf muscle tenderness. Toomey<sup>126</sup> treated paralysis of the facial nerve with *infrared heat* and *galvanism* with favorable results. The tungsten lamp was applied 18 inches away from the patient, the eyes always being covered. Each application of the rays lasted 30 minutes. In addition, involuntary movement of the muscles was accomplished by the use of the galvanic current. Twenty or 30 contractions were obtained during the course of a minute or two. This was done every day.

**Herpes Zoster**—Taterka and O'Sullivan<sup>127</sup> report two cases of herpes zoster with motor complications. Disregarding the more frequent cases of involvement of the cranial nerves in the course of this disease (otic zoster with facial palsy or ophthalmic zoster with oculomotor palsy), they were able to collect 42 cases with motor complications. Paralysis of muscles of the upper extremity occurred in 20 patients. In the majority of these the deltoid muscle was affected. In a few cases almost all the muscles of the arm were paralyzed. The trunk muscles were affected in 18 cases. The zoster eruption preceded the paralysis in about three-fourths of the cases. It followed the paralysis in one-fourth. In their two cases the muscles mainly affected were the quadriceps and deltoid, respectively. In one case there occurred fascicular and fibrillary twitchings. Parry and Laszlo<sup>128</sup> report a case of retrobulbar neuritis and one of sixth nerve paresis which complicated herpes zoster ophthalmicus in both. Stöckly<sup>129</sup> found *ergotamine tartrate* highly effective in the treatment of herpes zoster. He gave 0.5 cc. (8 minims) on the first day and 1 cc. (16 minims) daily until an effect could be noticed and then resumed the 0.5 cc. (8



minims) dose. The total dose varied between 4.5 and 6 cc. (72 and 90 minims). Lillie<sup>130</sup> found that the institution of *smallpox vaccination* early in herpes zoster ophthalmicus was efficacious in relieving both the subjective and objective phases of the disease. He gave vaccinations every fourth day for a series of four in one group of cases and every seventh day for a series of four or five in another group. The improvement occurred, regardless of the duration of the disease and the type of the previously instituted treatment.

### MULTIPLE SCLEROSIS

McIntyre and McIntyre<sup>131</sup> made a clinical study of multiple sclerosis, based on the life charts of 55 patients. Three clinical types of disseminated sclerosis were recognized: the acute, the remittent, and the chronic progressive. Twenty-seven patients had optic neuritis at some stage of their disease. In only one patient were both optic nerves affected at the same time. The prognosis for the optic neuritis in this condition is generally good; only one of the patients became totally blind. Optic neuritis may usher in the disease or may occur later in its course, years after other episodes have supervened. Seven patients showed visible swelling of the optic nerve. The prognosis is good for the individual attack in the remittent form of the disease. The prognosis for life is good in the remittent and chronic progressive forms. The prognosis for life in the acute form is not good. Patients with the remittent type of the illness may be able to lead useful lives for many years; in rare instances complete recovery occurs. Apoplectic episodes were experienced by 12 of 50 patients with the remittent type. They found no type of therapy advocated at present to be of any value.

### MYELITIS

Tick paralysis is a disease of animals and man consequent to the bite of ticks of various genera, most common of which is an American dog tick (*Dermacentor variabilis* Say) and the Rocky Mountain wood tick (*Dermacentor andersoni* Stiles). The disease is characterized by a striking neurologic syndrome, the outstanding symptoms of which are: (1) Ascending flaccid paralysis of Landry's type; (2) sensory changes which may or may not accompany the paralysis, and (3) incoördination. The paralysis progresses rapidly, ascends from the lower to the upper extremities and thence to the medullary and pontine structures. If the tick is not removed before medullary symptoms appear, death may result from respiratory paralysis. Recovery is the rule when the tick is removed from its victim before signs of bulbar paralysis have developed. The disease may be ushered in with severe ataxia, asynergia, and paresthesias. Elevation of temperature and convulsions in children have also been reported in some cases. The spinal fluid, in the few cases in which it was examined, was negative. Abbott<sup>132, 133</sup> reviews the subject and emphasizes its occurrence in the northwestern part of the United States and Canada. It is a condition which most commonly affects infants and children, though it does occur in adults. It is now believed that the tick injects some toxin into the host which causes the neurologic symptoms. The most important aspect of treatment is to think of tick paralysis whenever a patient presents himself with an ascending paralysis of Landry's type. Once this is accomplished it is a simple matter to look for the tick concealed in the scalp, ears, axilla, under the breasts, in the groins and perineum, and to remove it immediately by gentle traction. DeSanctis and di Sant'Agnese<sup>134</sup> report

a case which occurred in New York in a three-year-old girl. The child was markedly ataxic and incoördinate in her movements. All symptoms soon disappeared after a tick was removed from her scalp in the occipital region.

### VITAMINS IN NEUROLOGIC DISEASES

Williams and his colleagues<sup>135</sup> restricted the intake of *thiamine* in the diet of two human volunteers to 0.2 mg. a day (0.1 mg. for each thousand calories) for 120 days. Symptoms and signs of thiamine deficiency were manifested as early as the thirtieth day of restriction. The first objective evidence of abnormality consisted of a decrease in the urinary excretion of thiamine. At the fiftieth day anorexia and weakness had become more severe and the subjects complained of paresthesia of the legs. Later there was objective evidence of dysfunction of nervous pathways and after 110 days of restriction polyneuropathy became clearly apparent in both subjects. The neuropathy consisted of defects of sensory nervous pathways, loss of tendon reflexes and paralysis of muscles of the legs, which responded in both patients to administration of large doses of thiamine, but only after many weeks, and in one case incompletely after four months of continuous treatment. Loughlin *et al.*<sup>136</sup> reported the effects of *vitamin B therapy* in 22 unselected patients with paralysis agitans. They found no objective improvement in this group. The psychic manifestations of pellagra, as Sydenstricker<sup>137</sup> points out, can simulate neuroses and most of the well-known functional, toxic, and organic psychoses. The early symptoms are similar to those produced experimentally by deficiency of thiamine (vitamin B<sub>1</sub>), including lassitude, apprehension, mental

retardation, depression, and loss of memory for recent events, but in the patient suffering from pellagra these symptoms respond to therapy with *nicotinic acid* and not with vitamin B<sub>1</sub>. As Sydenstricker and others have pointed out, vitamin deficiencies are usually multiple and this applies particularly to deficiencies of B complex group. Moreover, administration of one member of this complex may precipitate signs of deficiency of others. Therefore, therapy must not in general be restricted to one vitamin. For the immediate treatment in the encephalopathies due to nicotinic acid deficiency, it is essential to administer that substance at once and in large doses. Sydenstricker advises 100 mg. of *nicotinic acid (niacin)* every hour for 10 hours during the first two days. He states that most patients improve greatly within 48 hours of the onset of treatment. Aring<sup>138</sup> reviewed the use of vitamins in clinical neurology in a comprehensive essay. He found that pellagrous polyneuritis responded readily to small doses of vitamin B<sub>1</sub> (5 mg. by mouth, three times a day) if there is a normal intestinal absorption. A syndrome characterized by clouding of consciousness, cogwheel rigidities of the extremities, the infantile sucking and grasping reflexes in persons chronically addicted to alcohol often responds to treatment by *hydration* and *nicotinic acid*. The Wernicke syndrome, which in most cases is constituted of ophthalmoplegia, polyneuritis, changing levels of consciousness, and mental abnormality, is a nonspecific syndrome and is the result of a severe nutritional deficiency. It is most frequently seen in persons addicted to alcohol. It may also terminate other toxic and wasting diseases associated with gastrointestinal disturbances. Thus, Gill and McCall<sup>139</sup> reported the case of a man suffering from cancer of

the stomach who died with Wernicke's encephalopathy. Epileptiform convulsions occurred during this illness. At necropsy a Wernicke lesion was found in the cerebral cortex. Aring reports that in some cases of migraine good results may be obtained with an average monthly dose of 350 to 450 mg. of thiamine given parenterally, with initial injections of 30 to 90 mg. given daily. The frequency of the injection was reduced over a period of about three months. If no favorable result was obtained in four weeks, 15 U.S.P. units of liver extract were administered parenterally once or twice a week. To terminate an attack of migraine, 60 to 120 mg. of thiamine were given intravenously or intramuscularly. He states that in neurologic diseases vitamin B factors should be given in large doses parenterally (*thiamine*, 25 mg. three times a day; *nicotinic acid*, 100 mg. six times a day; *nicotinic acid amide*, if no vasodilatation is desired, 100 mg. six times a day. *Vitamin B<sub>6</sub>* 50 mg. twice a day) in the early days of the therapy. When the desired result is initiated oral therapy may be resorted to with maintenance doses of vitamin B factors. A generous, well-balanced *diet* is an important factor. One method of assuring an adequate supply of most vitamin B complex factors parenterally is to give *liver extract* intramuscularly. It is suggested that an amount of liver extract equivalent to 15 U.S.P. units every four weeks should be used.

Needles<sup>140</sup> studied seven cases of diabetic neuritis before and after therapy with *thiamine*. In none was any improvement noted; in two, progression of the neurologic symptoms occurred. He concluded that in diabetic neuritis the metabolism of vitamin B<sub>1</sub> does not vary significantly from the normal. Davison<sup>141</sup> reported that of 10 cases of amyotrophic

lateral sclerosis treated with *vitamin E* and *alpha tocopherol 9* failed to respond clinically. Zech and Telford<sup>142</sup> likewise report that massive doses of *vitamin E* had no effect on the progression of symptoms in a series of patients with amyotrophic lateral sclerosis.

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## PSYCHIATRY

*Edited by* KENNETH E. APPEL, M.D., PH.D., Sc.D.

### MILITARY PSYCHIATRY\*

LIEUTENANT MANUEL M. PEARSON, MC-V(S), USNR

\*The views and opinions contained herein are the private ones of the author and are not to be construed as official or reflecting the views of the Navy Department or the Naval service at large.

The "war on nerves" has produced many new contributions in the etiology, terminology, symptomatology, therapy, and prognosis in mental illness observed under actual combat conditions. The active participation of the armed forces of the United States for the first time in this war and the emotional effects on the serviceman all the way from actual combat to prolonged operational activities have given psychiatrists many valuable

opportunities to study and record observations essential to the future knowledge and care of psychiatric casualties.

The importance of psychiatry in this World War II is incontestable. Strecker calls psychiatry "problem number one in World War II." At the induction centers rejections for neuropsychiatric reasons account for approximately 12 per cent., According to Halloran and Farrell,<sup>1</sup> 6 per cent of all patients remaining

in Army Hospitals are neuropsychiatric; 15 to 20 per cent of those reaching this country as casualties are neuropsychiatric, and "thus far the actual *ratio* of neuropsychiatric disorders to *all casualties* has been *about 5 per cent.*" It can be predicted with fair certainty that these percentages will all increase as the results of the increasing tempo of actual combat participation by our troops.

Interesting and equally important names have cropped up in the various branches of military activities to describe the traumatic war neuroses. The term "shell shock" is outdated and replaced by names such as "combat fatigue," "flight fatigue," "flying stress," "convoy fatigue," "operational fatigue," "nostalgia," and "separation neurosis." In an effort to combine dynamics with nosology, these newer terms are extremely important.

It is generally agreed that the most frequent form of psychiatric problem in military psychiatry is the psychoneurotic.<sup>1, 2</sup> The psychoses occurring under combat conditions are as relatively rare as the psychoneuroses are common, although it is pointed out that the early picture of a severe traumatic neurosis may be practically indistinguishable from a psychotic episode. Apparently it is far simpler to eliminate the potentially psychotic at the induction centers, training stations, boot camps, and staging areas than it is to detect the future psychoneurotic casualty. The constitutional psychopathic states constitute the second largest group in the Navy in wartime,<sup>2</sup> and these patients present the most baffling and demoralizing problem for the armed forces because of the refractoriness to therapy. Most observers agree that the military malingerer is fundamentally a psychopathic personality and therefore a breeder of poor morale, a military and hospital parasite, and a potential prey for foreign agents (Brussel<sup>3</sup>

and Good<sup>4</sup>). Needless to say, the malingerer should be prevented from getting into the armed forces or immediately returned to his civilian status.

**Combat Fatigue**—By far, the most challenging and most dramatic type of psychiatric illness in war is the traumatic neurosis, or combat fatigue. It comprises a syndrome peculiar to war and yet similar in the personnel of the army, navy, air corps, or merchant marine despite the variations in the activities of these divisions. Raines and Kolb,<sup>5</sup> in an excellent contribution, have outlined the characteristics of this common syndrome in the following way:

1. Repetitious catastrophic nightmares.
2. The "startle reaction" (hypersensitivity to noise).
3. A subtle personality change.
4. A guilt reaction with emotional depression.

They emphasize the fact that combat fatigue occurs in the previously stable, well-integrated personality, and seek to differentiate psychoneurosis and combat fatigue. "It is our belief that the psychological mechanisms associated with traumatic neurosis are as fundamental as to be present in all men and are of concern only in determining the extent of the neurotic responses, not its content." "The traumatically determined emotional disturbance goes no further than these symptoms. The rest goes into psychoneurosis."

The occurrence of neurotic symptoms in a previously stable person is a remarkable fact, these authors state, and proceed to show that their patients have none of the personality traits common to the future psychoneurotic, such as early evidences of emotional maladjustments, immaturity, childhood insecurity, or parental rejection.

**Etiology**—The etiology of the war neurosis has received a considerable

amount of discussion. Parsons<sup>6</sup> outlines the stresses to which these patients were subjected: (1) Separation from home, familiar environs, and the personal reassurance of the family; (2) strange occupations; (3) large responsibilities (in the case of officers); (4) fatigue; (5) impersonality of environment; (6) regulation of activities with loss of personal liberties; (7) strict accountability, and (8) anticipation of personal injury or death.

Rado<sup>7</sup> emphasizes the breakdown of the personality function of "emergency control," the mechanism that sets to work to remove the individual from dangers. He feels that the most efficient technic for the soldier in resolving his conflict is to ignore the dangers around him and live under the illusion of his own invulnerability, and immortality. If he cannot do this, then the "emergency control" will be subjected to an excessive amount of stimulation that will eventually overwhelm the individual.

Fairbairn<sup>8</sup> introduces the concept of the "separation neurosis" with his belief that all psychopathological developments in the adult are based on a persistence of an exaggerated degree of the emotional dependence of childhood and infancy. He states that the capacity to endure danger varies with the extent to which the individual has outgrown the stage of infantile dependence. His observations include the great deal of "homesickness" and compulsiveness to return home in the war neurosis, or the consciously executed flight of the psychotic.

**Symptomatology** — The symptomatology in the war neuroses has demonstrated some interesting features. In contrast to World War I, the dramatic conversion symptoms of major hysteria are notable by their absence, replaced largely by anxiety states and psychosomatic disorders. Instead of a neurocir-

culatory asthenia,<sup>9</sup> or "soldier's heart" as a predominating syndrome, psychosomatic expressions through the gastrointestinal tract are the most frequent form of complaint.

The striking feature in the neuroses resulting from combat is the similarity of complaints and objective findings according to Smith<sup>10</sup>: headache, lowered threshold to sharp noises, periods of amnesia, sensory somatic complaints, marked muscular tonicity, functional palsies. The hypothesis is formulated that this type of neurosis results from *prolonged* combat and not from brief periods of combat experience. In Smith's group only 5 per cent of his patients came from the Pearl Harbor disaster, while 95 per cent came from Guadalcanal.

**Prophylaxis and Therapy**—The discussion of the therapy of war neurosis was divided into two varieties: prophylaxis and active therapy.

Porter<sup>11</sup> gives a list of traits which, if sufficiently numerous (six or more) in an individual's history, suggest the possible breakdown under stress: (1) Bedwetting beyond four years of age; (2) thumb-sucking or nail-biting beyond age of six years; (3) failure to engage in competitive games involving risk or injury; (4) tantrums in childhood; (5) abnormal shyness or sensitiveness; (6) preference for playing alone; (7) repeated grades, difficulty with teachers, chronic truancy; (8) abnormal fears; (9) shunning of girls after puberty; (10) faints; (11) sulkiness under discipline; (12) excessive automatic system reactions to emotion; (13) abnormal attachment to mother after puberty; (14) stammering; (15) obsessional traits.

Federn,<sup>12</sup> drawing from his experiences during World War I, observed that many soldiers who had been neurotic in civil life stood hardships bravely



for a long time but once they lost their self-control they were less able to return to their previous level of adjustment than those who had been previously healthy. He emphasizes the importance of acoustic hypersensitivity and feels that an immediate protection from noise for traumatized patients would be an effective treatment to prevent a longstanding neurosis.

Four relatively new forms of therapy are being utilized in the treatment of war neuroses. *Narcohypnosis*, or the use of intravenous barbiturates to initiate a hypnotic state, is being used extensively in order to allow the patient to abreact his traumatic experiences. *Sodium amytal* is one of the most popular barbiturates, but the newer ones such as *pentothal* are also being used. The therapist can reassure the patient about the rediscovered traumatic episodes that are often mixed with guilt feeling as well as utilize the semisleep state for suggestive therapy. It has even been suggested that patients may not only talk about their experiences but will actually act out these traumatic episodes.

Another method used is *narcosis* or the continuous sleep treatment. This method was used extensively on the patients after Dunkirk with reported excellent results.

*Electroshock* has also been tried with a fair amount of success in those patients who were quite depressed.

*Group psychotherapy* is the fourth type of newer therapeutic procedure tried. This consists of giving psychotherapy in either small or large groups. Group therapy introduces a didactic element and is educational in procedure (Sherman<sup>13</sup> and Rome<sup>14</sup>). The simplest, commonest language about combat fatigue is used to give the patient an intellectual insight into his difficulties. It is recognized that individual psycho-

therapy is too long and impractical so that this new type of treatment has been formulated. Rome states that: "Group psychotherapy must be lived in constantly . . . by a carefully scheduled 24-hour routine. Work, play, classes, recreation, meals, rest are organized on the group plan." The advantages are these: (1) The similarity of symptoms as a ticket of admission relieves the therapeutic burden from any one individual; (2) tensions based on feeling unique are dissipated; (3) stigma is ameliorated; (4) the doctor-patient relationship is eased; (5) emotional release is controlled; (6) a too penetrating analysis is precluded; (7) individual sessions may be added if so indicated; (8) a 24-hour schedule avoids undirected lulls; (9) monotony is avoided by presenting material familiar to the group in a variety of ways; (10) the method is an expedient one.

**Prognosis**—The prognosis in combat fatigue has received a great deal of attention. Apparently there are two forms of criteria used: (1) The improvement in symptoms; (2) the restoration of the patient to some form of duty. Strecker<sup>15</sup> makes these observations on the outlook for war neuroses: (a) The less stable previous personality, the more readily it will break down and the less likelihood of recovery; (b) the longer time before patient gets psychiatric help, the less chance for recovery; (c) the closer to zone of activity the patient is treated, the greater chance for return to duty; (d) the more prominent the physical, doctors, deprivation, lack of rest, exhaustion, etc., the better the prognosis; (e) prognosis is difficult because of the trouble in determining presence or absence of traumatic brain complications.

Raines and Kolb<sup>5</sup> believe that all true combat fatigue will recover in a comparatively short time with even relatively superficial therapy.

Sherman<sup>13</sup> is also impressed by the spontaneous healing tendency of the war neuroses.

Smith<sup>10</sup> states that very few of these cases of war neuroses can return to full duty. "Ten to 15 per cent were returned to limited duty and in some of these cases we are being disappointed by too prompt recurrence of tension and anxiety states . . . no one can say as yet whether they will be as usual and successful as they were before combat fatigue experience."

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## PSYCHIATRIC SOCIAL WORK

ELIZABETH H. ROSS, M.S.

EDITOR'S NOTE: *One of the difficulties of democracy is the lack of strong, central organization which insures the effective use of manpower. When emergencies arise, it takes time to organize effectively and use the well-trained personnel that exists. Notwithstanding the dearth of psychiatrists in view of the need in the present war emergency, it has been difficult to mobilize and make available psychiatric social workers to help in the handling of personal and emotional problems of the men in the services. Some trained workers are in the services and have been assigned to other work. Fortunately, steps have been taken to remedy this situation. A very important one was taken by General Hershey in 1943, providing medical-social histories at the induction centers. A man's social, vocational, and medical history often is the most important basis on which a physician determines the man's fitness for service. It may be much more important than the results of a brief psychiatric examination at the induction center. Furthermore, it is with regard to the social-vocational history that there is often a tendency towards misrepresentation. A social worker's history is of great help in doubtful cases.*

*Psychiatric social workers have recently been assigned to the Consultation Services, the Mental Hygiene Unit, and the Rehabilitation Centers. These steps are important ones aimed at the prevention of emotional and mental breakdowns.*

*The following account of the development of this work is one of the first to appear and it is of importance, obviously, to physicians in their local communities to know what the armed services are doing for their men and former patients in this regard. It will enable physicians to tell relatives of servicemen something definite to do, someone for the men to consult when problems and worries of a personal nature develop about which servicemen write home.*

By definition of the American Association of Psychiatric Social Workers "psychiatric social work practice occurs in hospitals, clinics, or under other psychiatric auspices, the essential purpose of which is to serve people with mental or emotional disturbances."

For the purpose of training workers in this field, there are ten schools which include psychiatric training in their curriculum. They are: The Schools of Social Work at Boston University, Catholic University of America; Smith, and Simmons Colleges; The Department of Social Welfare at the University of California; the School of Social Service Administration at the University of Chicago; Schools of Applied Social Sciences at the University of Pittsburgh and at Western Reserve University; and the New York and the Pennsylvania Schools of Social Work.

The American Red Cross has outstripped all other organizations, since the National Defense program, in seeking psychiatric social workers for assignment to military and naval hospitals and clinics. The foreign and domestic demands have been so great that, at a minimum, it would appear that the Red Cross could absorb all trained psychiatric social workers. By providing a Psychiatric Social Work Consultant on the Headquarters Staff, and similar positions in the area, it is attempting to cope with the increasing administrative as well as professional demands made by neuropsychiatry in its unprecedented military and naval services.

The United States Army established psychiatric social work as an official military job classification in the fall of 1943. Thus, for the first time, the Army has a mechanism (through SSN 263) for identifying civilian trained or experienced social workers among its personnel. The program is too new for much description

or prediction. It seems to be an expression not only of a recognized professional need by psychiatry, but an expression, too, of the mental hygiene concern of present-day military psychiatry. Initial assignments of psychiatric social workers have been to Consultation Services, Mental Hygiene Units, and Rehabilitation Centers where programs of prevention of psychic breakdowns, and the handling of incipient maladjustments to the Army, have been featured. Evidence suggests military intention for further use of psychiatric social workers, not only in hospitals offering neuropsychiatric services but also in psychiatric programs involving the salvage and Army reassignments on neuropsychiatric combat casualties.

The medical survey plan, announced by General Hershey late in 1943, provides for medical-social histories of inductees for the use of Induction Center psychiatrists. Such histories obtained by volunteer social and health workers assigned to local draft boards are geared solely to the psychiatrist's use in his individual examinations, and may not be used to effect classification. The task of learning pertinent data necessitates new learning and new disciplines by the social service in relation to psychiatry.

While military psychiatric social workers are specifically assigned to work with psychiatry, an appreciable number of civilian trained social workers have been given assignments under nonmedical auspices that permits the utilization of some of their civilian professional background. In Classification and Personnel, AGD jobs, whether as an interviewer or a Personnel Consultant, as an assistant to a chaplain, in the psychological testing services in an induction center, in Special services, and a dozen other Army jobs, there are chances to use a fraction of a social work background in helping

puzzled, worried, sick, and frantic men to find ways in which to isolate and attack those mental and emotional difficulties which may hamper such men from becoming good soldiers. What knowledge or skill such experienced social workers can use in nonsocial work military assignments depends on factors ranging from the soldier social worker's own capacity to the interest of his superior officers.

Military psychiatric social workers, with their psychiatrists, are having a chance to find out what is the maximum social service possible in medical situations, ranging from prisons to rehabilitation units, from hospitals to divisional psychiatry. In addition to civilian professional interest and background, many a military psychiatric social worker appears to consider the fact that he is a soldier, one of his chief assets in working with other soldiers. He not only represents the psychiatric services of his particular assignment but can speak as one soldier to another. He sees his primary responsibility as that of serving the Army, in his psychiatric setting, for Army purposes. Thus, no matter what his personal feelings are towards an individual soldier's difficulties, he holds his relation to that soldier to the Army's resources, standards, and its expectation of men and of medical care. With such an attitude to guide their relations the social service worker, if he has had civilian training or experience in psychiatric social work, has some knowledge of social psychiatry, of the social evidences, and effect on social capacities, of various mental and emotional disorders. If he has not learned much of social psychiatry prior to his military assignment, he is aware of great need to learn deeply and quickly the social implications of mental illness. He has no concern with diagnosis, not often

with interpretation. But he must know the kinds and range of deviations in personality and character if he is to meet soldier-patients fearlessly, purposefully, sensitively.

The military social workers' knowledge and skill may be used in taking histories, an art in itself. His aim would be to insure that the history-taking process made sense to the patient, that it engaged his active participation, that it gave the soldier a chance to express feelings as well as facts, and that as a result of it the soldier was readier to accept the situation he was in and more prepared to do something about it. The military social worker would, of course, gear the content of the history to material needed by the psychiatrist, but he would be anxious that the connection he made with the patient while obtaining personal and social data would give an honest conviction that what he thought and said and felt mattered towards the fullest understanding and possible resolution of his situation.

Psychiatric rehabilitation of civilians and of discharged soldiers is being regarded as a medical-social need which cannot be delayed pending the cessation of hostilities. In the public field, the Physical Rehabilitation Section of Vocational Rehabilitation, Federal Security Agency, began work in December, 1943, in conjunction with a State grant-in-aid program for the medical and psychiatric care of all civilians eligible under the Amendment to the Act of July, 1943.

The National Committee for Mental Hygiene, in its recently created Division on Rehabilitation, has provided for the professional leadership of a psychiatrist, and the full-time service of a psychiatric social worker. Psychiatric centers for short term treatment of military rejectees, dischargees, and of others have been launched in at least three cities and in

each case psychiatric social workers are members of the clinical teams.

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## GROUP PSYCHOTHERAPY

SAMUEL B. HADDEN, M.D.

EDITOR'S NOTE—*The war is forcing on psychiatrists the exploration of relatively new methods of therapy. Because of the depletion of physicians from communities due to the war, adequate treatment of the neuroses and psychoneuroses is less available. Because of the great number of neuroses appearing in the armed services, the supply of physicians equipped to treat them is insufficient. Group psychotherapy, therefore, has been stimulated. It helps to fulfill a manpower need. There are certain advantages to group psychotherapy in its own right, which have been, for the most part, overlooked and which Dr. Hadden in his review stresses. General practitioners should become familiar with this method of treating the neuroses, which are such a drain on their time and energy. It would be a great help if in communities of any size one or more centers for group psychotherapy could be established. Psychiatrists from state hospitals could conduct such conferences at regular intervals. Such a practice would help greatly in the diffusion into the community of a knowledge of practical psychology and mental hygiene.*

Dynamic psychiatry has advanced the treatment of the neuroses to a point where a large percentage can be restored to normal health but, unfortunately, an adequate program of psychotherapy is so time-consuming that it is available to but a small number of the neurotic individuals requiring assistance. No method of treatment in medicine can be considered successful while its cost is prohibitive or it is not available to all sufferers. At this time measures which promise to shorten the time and cost of adequate psychotherapy and make it available to the legions of sufferers deserve full investigation. Group or mass psychotherapy can make adequate care available to greater numbers of neurotic persons.

The treatment of mental illness by the group method is not a new one; in this country Dr. Joseph Pratt began classes ten years ago to teach tuberculous pa-

tients more about the disease so that their morale could be improved and so they might contribute more to their own recovery. The results were very encouraging and it was recognized that the psychotherapeutic effect of the group was one of the principal factors in producing the more satisfactory results. It was natural that Pratt and his associates would eventually use the method in treating psychoneuroses. Harris and Rhoades have employed the method with encouraging results. Others, notably Marsh, Lazell, Schilder, Altshuler, and Hadden,<sup>1</sup> have utilized the method in dealing with psychoneuroses. With those who have used the method there is almost universal agreement that it is as effective or possibly more effective than individual psychotherapeutic sessions, and despite wide variations in the method used, the results seem to be universally good.

Low<sup>2</sup> organizes his group in such a way that there are no formal lectures and little didactic material is presented. Klapman,<sup>3</sup> at the Chicago State Hospital, utilizes a fairly systematic series of lectures on psychodynamic principles as the basis for his group organization. This method the writer has found to be most satisfactory at the Presbyterian, University, and Philadelphia General Hospitals. Jacobson and Wright<sup>4</sup> have utilized a group session in which they have had the various patients perform standard test situations before the group. The simple test situation was to have the patient write the 26 letters of the alphabet as representing 26 discrete volitional acts. The patient is observed as he writes the letters on the blackboard at his own speed, using small script letters on all occasions. His attitude and behavior during the test are observed and analyzed. The test situation is varied by dictating the letters at a changeable rate, by having patient and therapist alternate in writing the letters, by saying them alternately, or by having the patient write with the left hand. Other variations of the writing procedure give the psychiatrist the opportunity of observing the patient under these various situations and having those of the group as well as the patient discuss the deviations from normal which the performance reveals. This method was utilized in a class of 73 institutionalized psychotic patients, and 32 were reported as recovered and paroled. An additional 12 were reported as markedly improved. This method seems a rather indirect one but the results obtained clearly indicate the value of group activities. In neurotic groups, the restoration of 60 to 70 per cent may be anticipated.

Marsh has elaborately organized group activities for hospitalized patients in which he includes lectures on psycho-

dynamics and principles of mental hygiene, with time also devoted to group discussions. The motto of Marsh is:

"By the crowd have they been broken;  
By the crowd shall they be healed."

Those utilizing the group method can fully realize the wisdom of this statement.

The greater number of those using the group method have relied upon some didactic approach as a means of informing the patient, and then utilizing questions and discussions by the patients to effect catharsis and reorientation. Some groups are organized in rather a formal way, with "set lectures" to a fixed group of patients. When free discussion is encouraged, the results appear to be more satisfactory. In the author's most effective groups,<sup>1</sup> new patients are accepted at any session, since doing so affords the opportunity of repeating those principles which it is desired that all patients understand. At each meeting it is advisable to indicate to the group that they were referred to the class only after thorough investigation had failed to reveal evidence of destructive disease of the organs which appeared to be sick. It should be emphasized that severe bodily disorder can be produced by emotion. Recollecting the physical discomforts of stage fright and the altered function which occurs from anger or other emotion fixes this in the patients' minds. At each session it is advisable to emphasize that symptoms produced by emotion are very real—not imagined; but since such symptoms are not due to destruction of organ tissue, they can be relieved by correction of the faulty emotional state. How experiences such as anxiety, worry, sorrow, remorse, frustration, guilt, anger, resentment, repression and others may not only produce physical symptoms but may alter personality should be made clear—always

using common examples and encouraging those in attendance to report their own views and experiences.

The didactic portion of a session might well be used to present some psychodynamic principle in detail. In simple language, explain some mechanism of the mind, using as examples manifestations that are readily recognizable. Encourage the patients to discuss these principles. It is surprising how readily they talk of their own problems and recognize their own deviations from the normal. They soon speak freely of their feelings and behavior, interpreting their actions in terms of their newly acquired knowledge. The importance of previous experience, especially the early home life, can be stressed as a major factor in determining personalities and behavior. Patients readily appreciate that faulty home guidance might have inadequately equipped them to compete with life, and they are soon prone to discuss unhealthy home conditions with a satisfactory objective attitude. Such discourses should be carefully guided and, where possible, patients who have benefitted by attendance drawn into the discussions to provide encouraging comment and parallel experiences. At some sessions, the history of a patient can be read without revealing the identity of the individual. The nature of the visceral complaints can be discussed and the emotional conflicts revealed in the history explained. Sometimes patients whose cases are being reported can be asked for comment. When, by this method, the situation is made less personal, a patient may acquire a more objective attitude. Through such discussions, patients may obtain suggestions which lead to the solution of their difficulties; at the least, they receive sympathy and encouragement to continue their efforts at self-improvement from the under-

standing and consideration expressed by others in the group.

In addition to a discussion of psychodynamic or psychotherapeutic principles, the relationship between physical tension and increased reactivity of the nervous system may be discussed and a few minutes be devoted to instruction in how to obtain relaxation of muscle tension. It is recommended that effort be made to relax muscles not in use, and to be certain to become relaxed before retiring, thus insuring more restful sleep. Relaxation creates an attitude more receptive to suggestion, and following it patients can be given advice about the necessity of adequate rest, the desirability of interesting themselves in new activities, of keeping occupied, of planning their days, and of exerting other efforts to live more effectively and enjoyably. The living of a life may be compared to the building of a home, ship, or other structure, and the necessity of following a plan for best results may be emphasized. Lines of poetry or inspiring thoughts may be presented for comment.

In the group those who are too self-conscious to participate during the session may be encouraged to question the veteran members of the class on any matter which comes to their mind. This encourages socialization, and the older members often date their own improvement from the time they tried to help someone else. In the group, patients quickly lose their sense of isolation, one of the most disturbing phases of their condition. The realistic revelations of other sufferers impress them; they lose their resentment at being considered neurotic and work eagerly to become more adequate and more competent persons. As insight develops, they become more effective members of the group and, eventually, social assets.



As experience with the method increases, results will naturally improve. At first, it may be difficult to combat the resentment which some patients show at being referred to a group rather than being dealt with individually. This difficulty will decrease as those who have benefitted lend encouragement to the newcomer and explain the benefits he may anticipate. Although the teacher avoids the use of the word "neurotic," patients will often use the term in referring to themselves, and it has helped those who have been called "neurotic" to regard the term not as an opprobrious epithet but rather as a medical condition.

The mechanisms that are quite apparently the effective ones in the class are the satiation of the individual's gregarious instinct by becoming a member of a group from which there does not emanate any hostility toward the individual and the loss of the sense of isolation encourages patients to verbalize and externalize some of their own hostility. When patients first report to the group, it is usual for them not to participate very actively in the discussion; but as the others revealingly discuss episodes in their early life which led to resentment, frustration, hostility, etc., the newer patients vicariously identify themselves with these individuals, and a method of group catharsis becomes apparent. Transference to the therapist is active but transference to the group as a whole or to individual members also occurs. At each session patients are encouraged to comment upon the effect which the acquisition of certain psychodynamic principles has had upon their thinking. In this way reorientation of the individual's thinking is accomplished. In a group, hope is soon established and this lends courage to the component members—there is something contagious

about the hopeful attitude in the group which stimulates members to improve.

Of the various conditions treated, the *anxiety states* are most consistently benefitted. *Frustration neuroses* and *neurotic depressions* react well, and many patients with states of *reactive depression* are helped. Marked relief is experienced in some *obsessive states*, since the innate exhibitionistic tendencies are undoubtedly gratified by group discussion and the mechanism of obsession appreciated. *Conversion hysterias* do not respond well and they are more prone to discontinue attendance than any other group. More consistent in attendance are the *hypochondriacs*, though the only benefit observed in this condition has been a diminution of their willingness to give "organ recitals" at every opportunity. Benefits to *psychotic patients* have been reported by Blackman,<sup>5</sup> Lazell, Marsh, and others.

Of particular interest is the utilization of the group as a means of treating *maladjusted, hostile problem children* by Slavson.<sup>6</sup> He made no use of lectures and the therapist in the group was at all times passive. The only restraint utilized was that which came from the group. In these groups the children were provided with materials for clay modeling, painting, etc., with an understanding they could do as they pleased. The freedom from restraint was a new situation to the children and they gradually activated their hostilities in acceptable ways through the guidance of the group rather than from the restraint of the therapist. The results were gratifying and it is of particular significance that by this method results were satisfactory in those with limited intelligence, while by the didactic method and its modifications the results seem to be directly proportionate to the intelligence of the individual.

The group method is suitable, if not ideal, for application in *military psychiatry*. Here we have men under similar conditions who have shared the same experiences and have had similar training and aims. These common factors quickly produce a group spirit that is a powerful force in effecting the desired end, recovery. Rome and Braceland<sup>7</sup> report the military application of the method as being very efficacious.

Men rejected or discharged by the armed services for psychoneurotic disabilities feel their rejection or discharge is a stigma from which they cannot recover. With the large number of rejections, some provision should be made to rehabilitate those smarting under denial of the privilege of defending their country. These boys constitute a special problem and the group method is ideal for their management.

The group clinic has stimulating possibilities as a means of teaching psychotherapeutic procedures to students. Interns and students alike have been enthusiastic about it as a teaching medium. At this time, when there is need for the rapid training of psychiatrists in the management of the neuroses, the group

method ought to be considered in such a program.

It cannot be too strongly stressed that this method does not rely upon a strong emotional appeal for its efficacy. It need not be a revival meeting type of session at which noble sentiments and stimulating pep talks are delivered. The sessions of the class should be meetings at which sound basic principles of psychodynamics and psychotherapy are presented in the language of the patients, and all methods used to benefit the patient in individual interviews can be employed in the group. Those in attendance who participate in the discussions usually lend clarity and force to the leader's efforts, so that results obtained rival those derived from private treatment.

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## ROLE OF PERSONALITY FACTORS IN THE ETIOLOGY OF PHYSICAL DISEASES

LOUIS H. TWYEFFORT, M.D.

Present-day medicine is placing increasing emphasis upon the rôle which emotional factors play in the causation of both "functional" illness and so-called "organic" illness. Among the emotional factors receiving considerable attention is the part played by the specific type of personality in predisposing an individual to specific clinical syndromes. The term "psychosomatic illness" is becoming more and more applied to those

many diseases whose exact etiology remained obscure as long as they were approached solely from the physical side without due evaluation of contributory emotional and personality factors. Such syndromes as peptic ulcer, thyrotoxicosis, essential hypertension, certain cases of asthma, etc., come under this heading.

The complex interrelationships of personality and disordered body functions have been extensively investigated of re-

cent years and some general conclusions are being advanced (Dunbar,<sup>1</sup> Weiss and English<sup>2</sup>). Inadequate evaluation of personality factors in these syndromes, with resulting inadequate treatment, may result in recurrence, chronic ill health, or invalidism.

The general concept of personality includes the individual's "*characteristic ways*" of coping with life-situations making for conflict and requiring adjustment. Extensive investigation of the total personality is bringing to light the specific behavior patterns established in earliest childhood tending to be accompanied by specific physiological responses. Furthermore, differing types of emotional conflict (the "*focal conflict*") appear to be attended by specific physiological responses which may present a definite specificity, depending upon the exact nature of the conflict. These behavior patterns tend to be determined by the varying "*character defenses*" which the individual sets up for coping with or evading emotional conflicts set up by adverse environmental factors or personality inadequacies. Differing character defenses will give rise to differing physiological concomitants.

Physiological patterns which are displayed in response to emotional conflicts are largely laid down during the earliest years of life. Although constitutional factors play a rôle, the infant's early life experiences appear to play an even more important rôle in determining the exact nature of the physiological responses. The young infant's reactions to his environment are largely physiological. During the first year of life, the feeding process constitutes the child's outstanding experience. When being fed, the child should find satisfaction for his two outstanding *basic needs*: Adequate nutrition and adequate affection. Frustration of these basic needs results

in the child's earliest emotional conflicts which then give rise to anxiety or hostility. These attitudes of fear or anger are expressed primarily in a physiological way since thought and speech are not yet developed. In early childhood, dysfunction of the intestinal tract may represent an emotional response to some thwarting experience. Vomiting may be an expression of dislike, diarrhea an expression of insecurity. A continued feeling of resentment and suppressed anger may contribute to constipation. Localized spasm of the intestinal tract in response to anxiety may produce pain. In older children, it is a well accepted fact that feelings of insecurity or of hostility may be directly related to recurring enuresis or soiling. The expression of strong feeling through other organ systems is likewise seen in such manifestations as breath-holding spells, temper tantrums, and habit spasms (tics). These various symptoms are illustrations of the fact that underlying attitudes possessing a strong emotional charge may find expression in specific physical symptoms.

When an individual's personality fails to "develop" at the same rate as his chronological or physical growth, he is often spoken of as showing "emotional immaturity." His emotional reactions or technics for dealing with the conflicts and adjustments involved in normal living remain immature or inadequate, and will tend to lead to those personality disorders referred to as the *psychoneuroses*. Thus there are people who will *continue* to exhibit involuntarily very primitive physiological reaction patterns in their responses to the stresses and strains of normal living. Thus many an individual may continue to react to his stressful environment principally through his intestinal tract, as does the infant or young child when

faced with similar conflicts. On the other hand, many individuals will progress fairly well in their "emotional development" until their adjustment to living becomes too conflictful, whereupon they may *regress* to earlier, more primitive, physiological responses to conflict. Such an expression of *regression* is quite in keeping with the concept emphasized by Sherrington in connection with the central nervous system—to the effect that when higher, more complexly organized, centers in the central nervous system are injured, lower and more primitive centers, which used to function at an earlier period in development, will now again take over.

**Organ Language** — Intensive study of the child's emotional life has shown that a child exposed to anxiety-producing experiences at a time when swallowing and digestive functions are of paramount importance, will later tend to show a disturbance of these functions when under adequate emotional strain. When exposed to similar experiences in later life, such a child is very likely to reproduce similar symptoms of dysfunction in the upper gastrointestinal tract. In accordance with this concept, the child can involuntarily "use" his bowel or bladder to express something he wants to say if he has not the words or the courage to say it openly. This is another example of so-called "*organ language*." Thus an attitude and a pattern of organ function may become *associated* and stored in the individual's unconscious as an automatic, nondeliberate pattern of reaction. Later, if hostility is felt (toward a person or toward a situation) and this emotion cannot be *adequately* expressed (in a socially acceptable manner), the individual may then unconsciously resort to the former childish physiological patterns of expressing such feeling, with appearance

of such symptoms as urinary urgency (a modified enuresis), bowel frequency, nausea, etc.

**"Vector Theory"** — Alexander<sup>3</sup> has emphasized the potential rôle which may be played by the very early emotional association between the act of being fed (nursed) and the associated satisfaction of the deep-seated instinctual longing to be loved and to be taken care of. There are many adults in whom analysis has revealed extremely strong but completely repressed *dependent tendencies* (wish to be loved; wish to be taken care of), which tendencies are rarely given into because of a neurotically exaggerated sense of shame or guilt. Such individuals may present an outward appearance of extreme self-sufficiency and self-reliance. This is the type of personality which recent studies have shown will tend toward functional disturbances of the upper intestinal tract (gastritis, duodenitis, peptic ulcer, etc.). Many such an individual will initially develop a chronic disturbance in secretory and motor functions of the stomach. Because of the early association between being fed and being taken care of, it is Alexander's belief that the *chronic frustration* of the individual's dependent tendencies may tend to overstimulate stomach functions. The frustrated "need to be taken care of" thus might play an important rôle in stirring up the early *physiological* corollaries of the passive state of food expectation, since at the stage of infancy the "wish to be loved" was customarily supplied at the same time as was "the wish to be fed." Thus specific emotional factors may conceivably be connected with the sequence of gastric physiological disturbances which in some individuals may result in ulcer formation.

As speech and complex thought develop in the growing child, new methods of handling emotional conflicts become

available — such as the mental mechanisms represented by *projection*, *rationalization*, *displacement* (especially seen in the formation of phobias), *repression*, *conversion*, etc. Basically, all mental mechanisms are processes for dealing with anxiety and dissatisfaction (anger) naturally inherent in every conflict. Thus the growing child's responses to serious conflict may show fewer purely physiological patterns of response.

**Conversion Symptoms (Conversion Hysteria) Versus Vegetative Neuroses (Anxiety State)** — Any repressed or restrained emotional tension strives to find expression through bodily channels. Alexander<sup>3</sup> points out the importance of differentiating between conflicts leading to neurotic symptoms expressed through the voluntary nervous system as against those expressed through the autonomic nervous system. The symptoms of conversion hysteria proper are actually symptoms expressed through the *voluntary* neuromuscular and sensory perceptive systems. In this connection it should be remembered that the original function of the voluntary nervous system is to express and relieve emotional tensions through action. Hysterical conversion symptoms consist of substitute expressions of emotional tension which cannot find *adequate* outlet through full-fledged motor behavior. They may be viewed as a symbolic expression of a well defined emotional conflict and actually are an *attempt* at relief of such tension. For instance, sexual excitation denied full expression through intercourse may express itself through some other type of motor innervation, such as hysterical convulsions imitating the muscular movements of intercourse. Or, a marked feeling of anger denied normal expression in the form of yelling, shouting, or striking, may result in symptom formation in

those organs used for the legitimate expression of rage, namely the larynx, and result in a hysterical aphonia. These substitute innervations never bring full relief. Frequently hysterical conversion symptoms will express at the same time *both* the repressed emotion *and* its rejection (*e. g.*, a soldier who in a bayonet charge develops a hysterical paralysis of the arm).

On the other hand, those psychogenic symptoms which occur in vegetative organs do not represent an attempt to express an emotion but only the physiological accompaniments of the repressed emotion. They are not substitutive expressions of repressed emotion as are conversion hysteria symptoms. Thus the symptoms of the vegetative neuroses (that is, of organs supplied by the autonomic nervous system) are frequently the normal physiological correlates of fear or anger. As symptoms they do *not* relieve suppressed fear or rage, but simply accompany these emotions. They represent the physiological adjustments of the organism to situations actually involving danger or viewed as dangerous. They are not substitute expressions of repressed emotions.

**Muscle Tension** — Another unconscious physiological defense mechanism is that of generalized *muscle tension* which may involve both the body's smooth and striated muscle structures. This form of physiological response is common in individuals who make use of such "character defenses" as evasion, submission, etc., with much accompanying repressed anger. As pointed out by Braatöy,<sup>4</sup> muscle tension can act as the physical expression of repressed emotion and serve as an unconscious means for the repression or "binding" of repressed aggressive attitudes. Chronic repressed emotions of hostility can be held in check unconsciously by muscular rigidity. This

may be a *valid* physical explanation of much neurotic pain, aches, and fatigue.

**"Vegetative Retreat"**—A further understanding of chronic vegetative innervations is offered by Alexander's<sup>3</sup> concept of "*vegetative retreat*." A well adjusted individual may be viewed as showing balanced activity between the two divisions of the autonomic nervous system (sympathetic and parasympathetic divisions). Outwardly directed active aggressive trends will result in a sustained excess tonus of the sympathetic-adrenal system. It is conceivable that an individual developing a neurotic adjustment to the responsibilities of day-to-day living may for a while show overactivity of the sympathetic-adrenal system as a concomitant of a temporary positive attack upon his conflicts. Conceivably he may break under an excessive load of responsibility and may then recoil from his habitual overactivity and "assume the vegetative mood of the state that accompanies digestion" (that is, continuous hyperactivity of the stomach). The result of this opposite attitude, one of retreat from responsibility, will be accompanied by an increased tonus of the vago-insular (parasympathetic) system and be accompanied by such hyperactivity of visceral organs as results from a preponderance of *parasympathetic* excitation (*e. g.*, hypersecretion of the stomach, hypermotility of the stomach, diarrhea, psychogenic hypoglycemia from functional hyperinsulinism, etc.). Alexander would tend to view this as a sort of "countercoup phenomenon"—a kind of exhaustion of sympathetic functions following sustained effort. This correlation between the individual's basic attitude toward his conflicts on a specificity in autonomic nervous system response has also been referred to by Bieber.<sup>5</sup> An underlying attitude whose unconscious aim is to overcome at all

costs the anticipated frustration set up by the conflict (an attitude of mastery toward the environmental situation) may be accompanied by autonomic phenomena of an excitatory sort. On the other hand, a defeatist attitude in connection with the conflict, or a feeling of total impotency toward it, may result in a general attitude of inhibition with associated inhibitions of autonomic functions, resulting in *inhibitory symptoms*, such as excessive sleep, loss of consciousness, catatonia, amenorrhea, functional constipation, etc. On the other hand, an attitude of continuing attempted mastery of such conflicts might express itself *via* the autonomic nervous system through such symptoms as insomnia, tension of the somatic musculature, spasm in the intestinal tract, dysmenorrhea, profuse menstruation, diarrhea, etc.

### Choice of Symptoms; Choice of Site; Symptom Specificity

In the matter of "*choice of symptom*," that is, of the specific organ through which an emotional conflict will express itself, the exact determining factors are not yet quite clear. Such factors as the patient's early environmental experiences, his constitution, inherent organ weakness, early morbidity, pre-existing pathology may all play a part. But present experimental work strongly suggests that specific "vegetative dysfunction results from specific emotional constellations." Alexander is of the opinion that "just as the nature of the chronic unrelieved emotional state varies, so also will the corresponding vegetative disturbance vary." He would postulate a different psychology for each of such symptoms as gastric neurosis, emotional diarrhea, emotional constipation, cardiac dysfunction, asthma, functional glycosuria, etc.

**Personality in Gastrointestinal Disturbances** — The psychoanalytical studies which Alexander<sup>3</sup> and his associates have carried out on patients suffering from gastrointestinal disturbances, have resulted in the hypothesis that psychic factors which make for somatic disturbance are of a specific nature; that is, that certain emotional attitudes adopted by the patient toward his environment or toward his own person will produce disturbances of specific function. Since conscious emotions and tendencies can be freely expressed or relieved through the voluntary nervous system, they play only a subordinate rôle in the causation of such somatic symptoms. On the other hand, these symptoms are caused essentially by emotional attitudes that are repressed and unconscious to the patient. Such repressed tendencies lead to *chronic* innervations, causing chronic dysfunction of the organs under discussion. Conscious factors and acute traumatic situations play only a precipitating rôle in the causation of such symptoms.

**"Vector Theory"** — The intestinal tract has three main functions: (1) To receive, (2) to retain, (3) to eliminate or give out. In relation to his environment, the individual may show three basic attitudes: (1) A wish to receive (to be taken care of, to be loved, to be able to depend upon someone); (2) the wish to return values to the environment in terms of kindness or aggressiveness; (3) the wish to hold on to values and neither to take nor give. These basic attitudes, seen more clearly in the emotional reactions of children, could, according to this theory, find expression on a physiological level of intestinal functioning. These three elementary tendencies may find expression in this way if their normal expression through the voluntary motor system is inhibited

through inner conflicts. In the child one often sees that a frustrated need for affection will express itself in the form of compulsive eating, whereas resentment toward the environment may show itself in the act of soiling—"evacuation having the symbolic meaning of attack." In children, such symptoms constitute a further example of the individual using very primitive physiological reactions in an attempt to deal with a hostile environment. This hypothesis has been referred to as the "*Vector Theory*." Personalities tending toward disturbed function of the *stomach* may show a superficial attitude of activity, independence, and efficiency which covers up deep-seated repressed dependent wishes, while the accompanying physiological reactions are those of overactivity of the muscular and secretory elements of the stomach, as though this organ were being constantly prepared to receive food values. On the other hand, personalities tending toward chronic functional *constipation* frequently show stingy, miserly, over-possessive, retentive personality traits and a pessimistic attitude toward others characterized by spite and obstinacy. These attitudes may conceivably be expressing themselves somatically, using a regressive physiological pathway.

**Gastritis; Duodenitis and Peptic Ulcer**—Mittelman and Wolff<sup>6</sup> have carried out extensive personality studies in 30 cases showing these symptoms. Although the patients showed a wide range of personality features, they nevertheless commonly shared one characteristic: Behind a facade of independence and self-sufficiency, they gave evidence since early life of severe, repressed anxiety, feelings of helplessness, frustration, and extreme insecurity — feelings motivated by an intense passivity and a deep-seated wish to be taken care of and to be dependent on others, which feelings



had become intolerable to them in early life and had been *deeply repressed*. In actual laboratory experimentations with these patients, these workers were able to demonstrate that sudden fear in response to a dangerous situation which might elicit feelings of terror, helplessness, or objection in the subject, would be followed by symptoms revealing a preponderance of sympathetic innervation of gastric function (a sort of emergency reaction), whereas when the reaction to danger was one of chronic anxiety in which the will to resist survives (and may also be associated with feelings of resentment, hostility, or guilt), then there appeared a preponderance of parasympathetic predominance with the contrasting gastric symptomatology.

**Mucous Colitis**—Diarrhea is a well recognized infantile reaction to fear—another primitive physiological response to the threatening environment. Personality studies of patients suffering from mucous colitis have shown fairly consistent findings. Brown, Preu, and Sullivan (1938) lend emphasis to the following traits shown by these patients: Marked passivity, insecurity, emotional immaturity, complete failure of emancipation from parents, life-long dependencies upon parents or parental surrogates; egocentricity, emotional lability, and a tendency to become readily anxious. In practically all of their cases, an emotionally disturbing life experience had taken place just before the onset of the syndrome. In 30 cases there was not a single successful marriage or healthy sexual adjustment, nor was there an instance of complete emancipation from parental figures. White, Cobb, and Jones (1939), in a study of 60 cases, emphasized similar characteristic traits. In addition, these patients invariably appear overconscientious, show an extreme sensitivity to criticisms, and are unspar-

ing of themselves and of others in their demands for perfection. They show a marked tendency toward rumination and their obsessive methods of thinking make for constant preoccupation and a resulting prolongation of tension which seems to express itself physiologically in prolonged overactivity of the parasympathetic division of the autonomic nervous system.

Daniels,<sup>7</sup> as a result of psychoanalytical studies of such patients, emphasizes their very apparent masochistic trends and their concealed (repressed) sadistic tendencies. He would view their lower bowel symptoms as physiological expressions of fear and resentment, tendencies frequently expressed in this fashion on a physiological level by young children.

In connection with the possible expression of nervous tension through one or the other division of the autonomic nervous system, White, Cobb, and Jones (1939) call attention to how the sympathetic division seems reserved for the handling of dangerous *emergencies*, whereas the parasympathetic division shows overactivity in *chronic* conflicts. In mammals sudden retaliation to environmental danger is made possible by overactivity of the sympathetic division. But if retaliation does not seem possible, there results "a feeling of an entirely different character," accompanied by restlessness, or a mixture of anxiety and resentment with preponderance of parasympathetic innervations.

**Asthma**—A superficial personality study of 30 children showing asthma emphasizes the frequency with which specific personality features and special environmental difficulties appear closely related to the attacks. Those personality traits emphasized are aggression, domination, overanxiety, and especially insecurity. Many of the patients were only

children and reacted with extreme tension to overprotection and thwarting from oversolicitous and overanxious parents, or to tensions in the home frequently related to parental quarrels. Studies of a number of these patients with psychoanalytical technics add the following personality trends: Extreme ambition, hyperactivity, marked unconscious aggressive tendencies, and a tendency toward compulsive character (orderly, cleanliness, punctuality, fussiness, and meticulousness). Many of these patients showed hostility which seemed constantly on the point of going into action. The asthmatic symptoms themselves frequently appeared to possess an incapacitating and punitive quality (as far as their effect upon the patient is concerned), yet simultaneously also satisfy aggressive impulses (because of their distressing effect upon oversolicitous onlookers).

French, as part of his psychoanalytical studies of such patients, has raised the question as to whether "emotional situations which seem to precipitate the attack present any specific common characteristic." He and other workers who have analyzed these cases, feel that the common features in emotional situations which seem to precipitate many of the attacks, consist of exposure to a temptation which would estrange the patient from a parental figure—usually the mother or a mother substitute. The central danger is that of possible loss of the parent's love. Added confirmation seems present in the types of dreams which frequently precede nocturnal attacks of asthma. The dangerous situation may consist of some sexual temptation; the birth of a younger child; the discovery that the mother is pregnant, etc. From such dreams the patient often awakens with an urge to confess. French remarks, "confession is a defense that

utilizes speech and speech is a respiratory mechanism." For him the asthma attack is a regressive physiological symptom and a sort of equivalent of a cry of anxiety or rage which has been inhibited and repressed. In infancy the child separated from its mother will cry. Some of these patients report not having been able to shed tears for years. As analysis progresses, cessation of an attack may be followed by the appearance of crying in its place. Thus French views the acute attack as occurring in the place of a repressed cry in reaction to a temptation that threatens the patient with loss of the mother's love. Considered from this point of view, the asthma attack may be the result of *regression* to a very primitive physiological pattern of responding to environmental danger. French emphasizes that the precipitating situation seems to be not the actual fact of potential separation from the mother, but the indecision and conflict which result from the urge to cling to the mother and the need to separate from her, necessitated by any development of more mature attitudes. Alexander claims that in their unconscious tendencies these patients show an even more primitive dependency upon the mother than do gastrointestinal cases with their "oral receptive" attitude. Their type of unconscious dependence is even more primitive, and centers around deep-seated wishes to lean upon the mother and even to hide within her (as against the oral dependent wish to receive from her). This primitive instinctual yearning for the mother tends to be confirmed by the great number of intrauterine fantasies which appear in the dreams of such patients.

**Allergy**—Saul<sup>8</sup> advances a theory concerning the psychological determination of various specific symptoms in allergic conditions. His concepts, presented

in psychoanalytical terminology, can be summarized as follows: *Common colds* of a noninfectious sort may appear in connection with situations in which patients suffer from an intensification of frustration of passive, receptive wishes—usually with a prominent oral component. These colds sometimes disappear dramatically with the development of insight or with the alleviation of the frustration. He would view the congestion in the nose in such cases as representing “a chronic tendency to cry for mother.”

**Hay Fever**—In the nasal manifestations of *hay fever*, Saul feels that one contributory factor is presented by a “libidinal desire which is repressed and which affects the nasal mucosa.” Such libidinal longings may be connected with suppression of olfactory curiosity. Wilson<sup>15</sup> recalls the important rôle played by olfactory experiences in animals in connection with the detection of danger, in the maintenance of life (securing food), and in the mating experience. In the regressive psychoses, olfactory hallucinations are common as well as preoccupation with olfactory means of obtaining sensory satisfaction. He would view “the psychological component of the hay fever symptoms as a result of unsuccessful olfactory repression.” Such unsatisfactory repression may come in the wake of unsatisfied, thwarted, and inhibited sexual curiosity. A child reared in an atmosphere conducive to repression of sexual curiosity may become encouraged in indulgence in olfactory perception. With the threatening emergence into consciousness of the repressed curiosity (so intimately connected with fear and sexual impulses), after the more primitive olfactory curiosity has been substituted for visual curiosity (through a regressive displacement mechanism), the olfactory areas become overcharged,

leading to *inhibition*. Thus acute rhinitis may develop on the basis of a conversion symptom. Inflammation of the nasal mucous membrane and of the conjunctiva of the eye then appear in order to inhibit or destroy the sense of smell as well as the optic sensitivity. The eyes and the nose (organs of sexual curiosity), through the conversion symptom mechanism, assume the character of sexually stimulated erotic organs. Thus a disturbance of the sense of smell may be viewed in certain cases as a *regressive solution* to dangerous curiosity.

**Urticaria**—Saul and Bernstein<sup>10</sup> have evaluated the emotional settings of attacks of *urticaria*. In the cases studied, the personality traits most in evidence center around excessive masochism and repressed exhibitionism. The emotional situations for the attacks of *urticaria* seemed specific in terms of: (1) The intense thwartings of an underlying wish for love and help which were (2) intensively aroused but in the *very moment of frustration*. The frustration theme centers around “almost but not quite” situations. In the cases cited certain *reciprocal relationships* were frequently encountered. If the specific emotional conflict arose but if the patient wept he would have no *urticaria*. On the other hand, attacks of *urticaria* were usually terminated by weeping. If weeping were suppressed an attack would frequently occur. Certain repetitive dreams of frustration would tend to end either with weeping *or* with *urticaria*. In these cases it was felt that the skin was chosen as the *site* of symptom formation, probably because of a combination of circumstances: (1) The intensity of the exhibitionistic component of the personality; (2) the heightened eroticism of the skin (because of aroused sexual longings which, because of the patient's guilt, could not be satisfied through genital

sexual activity); (3) masochistic experiences in earlier life in which a sexually tinged type of pleasure had been achieved through skin sensory experiences. Saul views the physiology of emotional urticaria as occurring through an overactivity of the parasympathetic division of the autonomic nervous system. The appearance of such a symptom at a time when increased demands are made on the patient would place it in the category of "*regressive responses*." In these cases, demands for exertion result in discharge of excitation not by the sympathetic division as normally, but by the parasympathetic division signifying "a retreat from effort" (*c.f.* Alexander, above).

**Essential Hypertension**—In cases of essential hypertension a number of authors have reported *specific focal conflicts* and *specific character defenses* unconsciously set up by the individual in an attempt to deal with the underlying conflicts. These individuals suffer from chronic, inhibited, hostile impulses which in early childhood frequently found expression in temper tantrums but later became repressed, or might occasionally become indirectly manifest in occasional explosive outbursts of anger or less obvious acts of rebellion. They invariably present an exterior of gentleness, self-control, and reserve which acts as a cover-over for the underlying intense hostility. Their *main defense* is expressed somatically in the form of generalized muscular tension which principally affects the tonus of their cardiovascular systems. Although they show few outspoken neurotic symptoms, their underlying hostility is frequently "splinted" on the psychic level by the presence of a long-standing "compulsive type of character." Another character-defense is their marked submission to authority (strong superego). Unwittingly such patients often give expression to the under-

lying conflict in such statements as "I always say 'yes,' I don't know why. Afterwards I am furious." The early origin of their hostility is explained on the following basis: In early childhood as a result of the parent-child relationship, they have developed attitudes of extreme submissiveness which reflects itself in passive, dependent, receptive tendencies. As they mature, these individuals in their overt behavior may develop overcompensatory competitive aggressive attitudes which they are unable consistently to maintain. When, due to external thwarting by circumstances or due to internal inhibitions determined by feelings of guilt, pride, ambition, narcissism, etc., their extreme dependent attitudes are not satisfied; they react with extreme, repressed anger at this frustration. This conflict between passive and aggressive tendencies is a common, central conflict in many psychoneurotics who have normal blood pressure levels. Nevertheless, this specific nuclear-complex of the hypertensive individual differs in that he is unable to accept either opposing tendency (*i. e.*, he is unable to accept his passivity or express his hostility). He is neither weak nor aggressively hostile but finds himself blocked in both directions. Nor is his hostility "bound" by any organized neurosis. Many individuals will show a conflict centering around this submissiveness without any blood pressure involvement. These individuals on the other hand appear to have handled their conflict in other ways: through acceptance of their submissiveness; or by overcompensating in other ways; or through the fact that their resentment becomes bound up in symptoms of some organized neurosis. During psychoanalytical treatment, as the unconscious conflicts are brought to consciousness and so can be worked through, the physiological defenses against repressed anger

(muscular hypertension) become no longer necessary and the blood pressure levels return towards normal. In the course of treatment, during periods when either the repressed aggression or the overt dependency trends become temporarily satisfied, the blood pressure likewise is reported as becoming markedly lowered.

### "Chronic Diseases"

**Cardiovascular Diseases; Rheumatism; Diabetes** — In spite of the tremendous progress made by medicine in the past generation, the bulk of morbidity is still due to illnesses concerning the etiology of which little is known. According to health surveys, the most common "chronic diseases," in terms of number of cases, consist of rheumatism, heart disease, arteriosclerosis, and hypertension, in this order. There are over 14,000,000 sufferers of these specifically named diseases in the United States. Accordingly, it may be said that diseases of unknown cause (though the etiological hypotheses are multiple) account for the majority of illness in this country.

Dunbar<sup>1</sup> has just published the results of an extensive study of 1600 patients, intensively studied in terms of the physiological and psychological components of their illness. This survey covers a period of more than five years and the reported material relates specifically to cases of cardiovascular disease and of diabetes. Fracture cases were used as controls. Specific attention was paid to the following eight syndromes: hypertensive cardiovascular disease, coronary occlusion, anginal syndrome, rheumatic fever and rheumatoid arthritis, rheumatic heart disease and cardiac arrhythmias, recurring accidents.

The outstanding purpose of this study was an attempt to answer the questions, "Is there any *personality factor* that is to

any degree specific for one type of physiological disorder as compared to another?" "Are the *personality factors* found to be operative in a given illness in any way specific for the disease itself?" The specific personality picture associated with each syndrome turned out to be much more specific than had been anticipated. Not only is this true of the study of the personalities of these patients, but their reaction to illness, as well as to treatment (medical and psychological) revealed marked similarities among the members of each illness group and equally marked contrasts among the several groups. These findings apply not only for the cardiovascular and diabetic cases reported in this study, but likewise for the gastrointestinal and allergic cases which findings have not yet been published.

These studies were made on serial admissions, not merely on patients suspected of having emotional problems. The *psychic component* was primarily a reaction to the illness itself in only 5 per cent of the cases, whereas it appeared as a complicating factor affecting the course of the illness, and the response to treatment in 75 per cent of the cases. It assumed *demonstrable* etiological significance in the development of the illness in at least 50 per cent of the cases. It was felt that a large percentage of these patients were being kept ill unnecessarily by this (emotional) component of their illness. Unfortunately, most patients whose illness is predominantly conditioned by emotional factors admit of no such conflict, nor do they give evidence of such conflict when they are studied by the routine medical history technics of approach. In fact, they may give a superficial picture of normal life adjustment. In many of these cases the damaging emotional conflicts are operative on an unconscious level. A further merit of



In this general constellation *quantitative* factors are as important as *qualitative* factors. The various disease groups investigated showed a marked difference in these constellation components. The frequently asked question, "Why does everyone who goes through emotional stress and strain not develop illness?" depends for its answer upon these constellation interrelationships, of which the personality traits or "characteristic" ways of meeting difficulties are of special importance. Dunbar<sup>1</sup> feels that it is too early to state categorically that these personality traits may actually cause disease, but that it is not too early to suggest that these same personality traits are important *predisposing* factors.

**Focal Conflict**—By "*sphere of conflict*" or "*focal conflict*" is meant that particular aspect of adjustment to life in which the major frustrations have appeared. This particular conflict has often become chronic and most strongly repressed. Such conflict may center around the individual's reactions to authority, the urge to get to the top, the assumption of responsibility (examples of conflicts involving the so-called herd instinct); or conflicts centering around aggression-passivity, dependence versus independence (examples of conflicts centering around the instinct of self-preservation); or conflicts centering around the development of mature sexual attitudes (ambivalence in the sexual rôle, aggressive-passive attitudes); or conflicts relating to the individual's contacts with the outside world (narcissistic withdrawal versus desire to be effectual or admired).

In the constellation of factors pertinent to specific clinical syndromes, the patient's "character" or habitual ways of dealing with difficulties ("character defenses" or "behavior patterns") are of outstanding importance since psychologi-

cal attitudes may have their *specific physiological* expressions.

**Reaction-Patterns** — The behavior patterns or ways in which the patient deals with his difficulties will tend to center around one of the following general reaction-patterns: action, speech, or thought (including fantasy). In spite of the undoubted existence of an indefinite "constitutional factor," *the physiological accompaniments of the emotions aroused will be different*, depending upon whichever of the above general reaction-patterns predominates. When reactions to conflicts are largely through patterns of thought, one will naturally get the greatest likelihood of autonomic nervous system symptomatology. Dunbar quotes Sherrington's pertinent remarks in this connection: "Speech, since it provides some degree of externalization of energy, may be regarded as standing between musculo-skeletal behavior (*i. e.*, action) and thought, and is also a manifestation of partial motor inhibition. The degree of availability of these modes of cortical expression to the instinctual levels is in direct proportion to the degree of motor inhibition . . . yet the degree of relief of instinctual tension depends on the degree of sheer motor component in the expression. Thus, action gives the greatest relief; thought, or fantasy, the least. . . . Speech stands midway between them."

**"Acting Out" vs. "Pent Up" Tendencies**—In evaluating the part played by repressed emotions in illness, it is of fundamental importance to attempt to determine the degree to which a patient responds to his conflicts (1) in action, or (2) in thought (thinking, philosophizing, creation of fantasies). In either case the prominent pattern may be an attempt to (a) meet the situation; (b) to escape from it, or (c) to oscillate between these two courses of action. Some patients show a very marked "acting-out tend-



ency" (fracture cases especially) by which emotional conflicts are escaped from into action, and the patient will express his aggression in impulsive behavior which may lead to injury of others or of himself. On the other hand, other patients show a clear-cut "pent-up" tendency" (especially cardiovascular cases) in which aggression and resentment is, as it were, internalized and expressed somatically in the form of muscle tension. In this respect the body's musculature may be viewed as a sort of "characterological armor" by which instinctual aggressions can as it were be "splinted." This internalization of instinctual energy is not adequately appreciated in present-day medicine and as a result many clinical pictures showing autonomic nervous system overactivity, or underactivity, are improperly understood in terms of their true etiology. Thus, muscle tension can be viewed as one physiological means of keeping important emotional material under repression. When emotional conflicts are thus repressed and much hostility pent up, the tension can become driven inward and be an important factor contributing to syndromes resulting from hypertonicity or hyperactivity (constant or intermittent) of smooth muscle structures or secretory organs (as seen in essential hypertension, coronary and anginal syndromes, gastrointestinal disorders, cardiac arrhythmias, and disorders of the endocrine apparatus).

Extreme generalized tension in a patient may escape detection because of the patient's unconscious desire to keep the expression of his emotions under complete control. Nevertheless, in his casual, unguarded statements, the patient may give very significant clues pointing to the existence of these patterns of response to emotional conflicts. Very suggestive of the internalization of emotional conflicts are statements by the patient who says,

"I am never angry, I keep everything in; don't mind these tears—they mean nothing—I'm always affected that way"; "Peace at any price is my motto"; "I never let on to my husband"; "I've always had good control"; or the patient who seems to put forth all his efforts to endure and please, or who seems unnecessarily anxious not to make a nuisance of himself; or the patient who remarks, "I was very ambitious, but never let myself go," etc., or the wife who is known always to say "Yes" to her husband and drags around not feeling well. Thus, the patient's personality, his "characteristic" defenses or customary ways of dealing with conflict situations will have a very direct bearing upon his "*symptom pattern*"—that is, *the organization of his symptoms*, psychic and somatic, and the relationships between them. Emotional factors may be strongly suspected as contributing to the past and present tendencies to illness if his history shows a long series of disorders in which disturbances in muscle tonus, or secretion, or circulation are prominent (*e. g.*, colitis, hypertension, muscle spasm, gallbladder dysfunction, etc.). Also if the disturbances of secretion or muscle tension are out of proportion to the rest of the symptoms, or to the obvious somatic factor apparent. Furthermore, emotional factors are strongly to be suspected if several systems are involved simultaneously (such as a tendency to hypertension associated with chronic constipation and general increased muscle tonus). The nature of the accompanying psychic symptomatology may be an index to the prominence of action *versus* fantasy, whose important correlates have been referred to. Does the patient give evidence of anxiety or active fantasies? Does he report elaborate dreams, nightmares, compulsions, phobias? Or is he relatively inarticulate, casual, and reticent

about his personal problems, seeming more to be a person of action rather than of thought? Does he deny being nervous, given an external appearance of quiet control while showing indirect evidence of generalized tension?

**Shift in Symptom Location**—It must also be remembered that a patient suffering from an emotionally determined functional disorder may frequently show a shift in the manner of expression of his emotional tensions (a) either from one organ system to another, or (b) from somatic to psychic manifestations, and *vice versa*. These variations in the physiological manner of expression of emotional conflicts may be connected with the patient's using *new* psychological defenses in trying to cope with his focal conflicts. These shifts frequently occur when a patient has been surgically or pharmacologically relieved of that particular organ through whose derangement underlying emotional conflict is making itself known to the environment.

**"Pseudo-Heridity"**—In connection with the environmental happenings which enter into the "constellation" of factors making for a special type of syndrome, much evidence is being accumulated bearing upon factors which in the past have often been confused with true heredity. Dunbar's studies show quite conclusively the important rôle played by *exposure* ("pseudo-heridity") to a similar syndrome in relatives, or nonblood relatives, or in friends, at an earlier life period. This matter of exposure to a syndrome seemed to play a more important rôle than did actual heredity, especially in cases with cardiovascular syndromes. Naturally, the matter of exposure may act by way of psychological suggestion, but much more important is the fact that such exposure usually implies that the patient has been in constant proximity to those specific reaction patterns in

others which tend to lead to the eventual development of these syndromes, and by unconscious example has adopted those reaction patterns himself. In the matter of such exposure, the developmental age period when such exposure occurred, as well as the patient's attitudes towards the ill person, are of extreme importance. Such exposure to illness during the first five years of life may have especial significance.

**Personality Profiles**—Illustrative of the constellation of factors which appear to make up the emotional factors and environmental conditions peculiar to specific syndromes, two of Dunbar's "personality profiles" are here listed in somewhat abbreviated form:

#### CORONARY OCCLUSION

*Personal Data:* Both parents typically strict; high marriage rate; many children; few divorces. *Health Record:* Bad previous illness history with predominance of autonomic nervous system symptoms. Tendency to self neglect. *Education:* Marked tendency to complete planned career; stick to one job; work to top. Executives, officials. *General Adjustment:* Respected; tendency to dominate. Rôle of exemplary husband and father combined with sense of frustration. Tend to emphasize sexual problems (overt anxiety). Hostile towards own father; passive though often hostile and fearful towards mother. Towards own family: attempt to be boss and carry burden combined with demand for care and attention. *Characteristic Behavior Pattern:* Compulsively consistent action; long hours, no vacation; tendency to seize authority; dislike of sharing responsibility; tend to attach emotion to ideals and goals. *Neurotic Traits:* Few in early life. Tendency to brood and keep troubles to self. *General Interests:* Little interest in sports; few hobbies; religious skepticism but marked interest in philosophy. *Life Situation Immediately Prior to Onset:* Exposure to shock especially in job or in relinquishment of authority. *Reaction to Illness:* Minimize symptoms; self neglect. *Area of Focal Conflict and Characteristic Reaction:* Attempt to be or to subdue authority; identification with authority; attempt to surpass authority.

## DIABETES

*Personal Data:* Subacute struggle with parents usually continued throughout life; males tend to remain unmarried; married males or females—few children, few actual divorces but many periods of living apart. *Health Record:* Good but women have poor pelvic histories. *General Adjustments:* Disinclination to assume responsibilities; unable to take initiative in important matters; difficulty in managing personal relationships. Marked social anxiety. Anxiety and inadequacy in sexual adjustments. Marked conflict between hatred of parents and submission. Similar attitudes toward spouse. *Characteristic Behavior Pattern:* Inability to follow any consistent course of action; isolation and indecision. *Neurotic Traits:* Childhood—temper tantrums, phobias, nightmares; adulthood—nervousness, depression, suspicious trends. *Interests:* Food; preoccupation with innumerable odd jobs; avoidance of competitive sports; little religious interest. *Life Situation Immediately Prior to Onset:* Long period of wear and tear including hard work; struggle with family and spouse. *Reaction to Illness:* Depression alternating with feeling of relief at having alibi for inadequacy. *Area of Focal Conflict and Characteristic Reaction:* Centers around assumption of responsibility (dependence versus independence; vacillation); sexual rôle (ambivalence; vacillation between male and female attributes. Inability to attain a mature sexual adjustment).

## Fracture Cases

Although at the beginning of Dunbar's study *fracture cases* were studied in terms of their personality so as to offer an expected normal control, investigation surprisingly disclosed that these persons have a significantly meaningful personality profile with many pathological implications. Although most people have always "assumed that accidents always happen by accident," insurance companies have for years insisted that only from 10 to 20 per cent of all accidents can be ascribed solely to mechanical causes. These studies have disclosed a definite accident diathesis. Of these fracture patients, 79 per cent have had two or more accidents, whereas of the pa-

tients showing the other syndromes under study, no more than 11 per cent of any one group had had two or more accidents. These fracture patients are relatively inarticulate and show a tendency to escape from an emotional conflict into action (with little tendency toward indulging in thought, fantasy, or brooding). If thwarted they tend to "do something" to modify the situation or to get away from it, instead of keeping their resentment bottled up. Their focal conflict is one of avoidance of authority.

## Combined or Overlapping Syndromes

Conceivably patients might suffer simultaneously or successively from two or more of the eight syndromes investigated. Of the 1600 patients reviewed, only 20 per cent suffered from two or more of the syndromes under discussion, and less than 1 per cent had suffered from three of such syndromes. With eight separate syndromes there is a mathematical possibility of 247 combinations. Yet in this series there were only 22 combinations of syndromes. That specific personality factors predispose to each syndrome is further suggested by the fact that there appears to be an absence of a chance distribution of overlapping syndromes and by the prevalence of particular kinds of combinations. These figures suggest that in the cases showing two or more syndromes the factor predisposing to *both* should be looked for. Such a common factor may exist in the *personality organization* of the patient—that is, in his *focal conflict* and *characteristic manner* of dealing with it, extending way back to his childhood.

Thus there may be a relationship between personality types and predisposition to a given syndrome. The area of focal conflict may be the same for two diseases found in combination, but the manner of reaction to the difficulty may

at times differ and this difference may be accompanied by a different syndrome. Judging by their life history, some patients give evidence of a rather complete change in their personality type and similarly in their major syndrome—but “the personality type in each case is appropriate to the syndrome *found at the time*.” Occasionally a given individual of one general personality type may have different illness syndromes accompanied by *particular* emotional tensions. “Hence the *same* illness syndromes may accompany a *specific* emotional tension in *different* personality types.”

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## SEX AND MARRIAGE

KENNETH E. APPEL, M.D.

Practitioners of medicine are often called upon to deal with problems and to answer questions which, in the narrow sense of the term, are not purely medical. This applies to parent-child relationships and attitudes towards sex and marriage. There have been published many books on this subject in the past 20 years, but the busy practitioner cannot go through the whole field and glean what is suitable for his particular problem. Fortunately, Levine<sup>1</sup> has written an unusually helpful book for physicians, which summarizes in many instances the best thinking on these subjects. His chapters on Marriage and Attitudes Toward Children ought to be required reading for all medical students, and certainly doctors would be greatly fortified by the knowledge summarized and presented in these chapters. Because of the importance of the subject we have presented, in brief, points emphasized by Levine in his chapter on Sex and Marriage. They pertain to matters about which practitioners are often questioned by their patients and about which there is considerable apprehension and misinformation.

Many patients believe that minor variations in the size of the sexual apparatus interfere with sexual satisfaction and pleasure. The fact is that the elasticity of the vagina is sufficient to take care of such minor variations in size of either the penis or of the vagina. Fears such as this are fundamentally illogical ones based on emotion rather than fact. They may be based on rumors and misinformation, or on the “small penis complex”—that is, the unjustified fear, from the feelings of childhood—that the penis has been injured by masturbation, or because of threats of injury to the penis or even on the unconscious wish in rare instances to have a small penis and thus remain a child. Many women expect damage to the genitalia in intercourse, with the idea that the vagina is too small to permit entrance of the penis.

Minor difficulties in sexual performance on the part of both men and women are normal and average. Particularly in the first year of marriage, some difficulties are almost universal—some frigidity on the part of the women and occasionally premature ejaculation or impotence

on the part of the men. It is important that the fear that this condition become permanent should be removed. Married people should be told that they must have some patience and tolerance of the fluctuations of the partner and that a perfectionistic attitude in this respect is a source of difficulty.

Many different forms of sexuality can be regarded as normal and mature, and not as perversions or deviations under certain circumstances. Because of the social and psychologic reactions to sexual impulses, patients who find they have impulses which might be those of deviation become much disturbed. They also make the mistake of regarding such impulses as synonymous with perversion. From the medical point of view there are many variations of sexual activity which are to be regarded as normal when these activities are *preliminary* to intercourse. It should be understood that these normal deviations do not result in physical injury. Such deviations from the point of view of maturity should be *mutually acceptable acts*—it is certainly not a part of mature marriage for one individual to force the other into unacceptable activity.

Human beings seem not to have such definite periodic fluctuations of sexual desire as do the lower animals, but they apparently do have some rhythm of desire. These fluctuations are found particularly in women and are usually related to the menstrual cycle. A knowledge of this fact may lead to an increase in the happiness of the sexual relationship—when sexual satisfaction can be had at a time of the increase in desire on the part of one of the individuals.

It is a fallacy to believe that one must have full sexual satisfaction in every sexual experience. There can be enough pleasure on the part of one, in the pleasure of the other, to make possible a

sufficient cooperation in a period of relative indifference.

In many marriages there is an overemphasis on sex as the indicator of the value of the individual, and sexual performance becomes to too great a degree a matter of pride rather than a matter of mutual satisfaction.

Masturbation does not lead to failure in coitus. Many people believe that masturbation prevents an adequate potency or response, or tends to cause a fixation of satisfaction on areas or actions other than those stimulated in coitus. Clinical experience indicates that this need not be considered as a practical issue. The evidence is that a large percentage of individuals have masturbated with some frequency and yet can have an adequate performance and satisfaction in coitus.

There need be no panic over past deviate experience. It is not true, as many patients believe, that a transient homosexual contact in the past will render a happy marriage impossible of attainment. All human beings are bisexual in varying proportions and some individuals who have had strong homosexual desires and experiences in the past will have as strong or even stronger heterosexual desires and satisfactions. In one study it was found that about 50 per cent of successfully married men and 25 per cent of successfully married women had transient homosexual experiences before marriage.

The relatively slower sexual responsiveness of women has been exaggerated as a factor in the production of nervousness. It is true that many women are unsatisfied after an intercourse in which the husband has not given adequate attention to the wife's pleasure, but it is not at all certain that this lack is a really serious or disturbing etiologic factor. This does not mean that the man should not do whatever he can to bring about satisfaction for his wife, either by pro-

longing the period of coitus or by stimulation before, during, or after coitus.

Marriage and sexuality are fundamentally matters of cooperation and mutual interest. The attitude that sex in marriage is the prerogative of the dominant male and that the woman's interest need not be considered is one that will lead, frequently, to dissatisfaction and unhappiness. Further, the attitude that sex is only an act of duty or submission on the part of the woman is usually an unhealthy one.

From the medical point of view it is possible to recommend an attitude of acceptance, particularly in marriage, of sexuality as something worth while, as something which is capable of beauty, as something not fundamentally dirty but as something which can be one of the decent, productive, stimulating, and fine things of life.

Hyposexuality (a lack of interest or a slight interest in sexuality) is not an indication of a higher type of personality as is claimed by many patients. Usually it is a sign of emotional conflict or immaturity.

Sexual activity and practices, urges, and disinclinations are not just matter of conscious, deliberate, voluntary control. Many factors or forces enter into sex practices, feelings, impulses, and thinking. Obviously, instinctive factors enter and they are not primarily rational. As a matter of fact too much intellect, reasoning, and the use of rules and advice, may interfere with the normal, wholesome carrying out of the sexual act. Childhood experiences and parental teaching are parts of the unconscious forces which modify our feeling, thinking, and practices in sex matters.

Fantasies in childhood often carry over and modify adult attitudes with regard to sex. Children build up fantasies, for example, to account for the differences

between the sexes. Girls may so envy what they consider the greater freedom of boys and their superior prowess that it develops unwholesome attitudes in the adult, which interfere with social and vocational adjustment and also with sexual marital adjustment. The girl's envy of the boy may lead to chronic depreciation of self (girlhood) and femininity. Along with this may go an attitude of antagonism, hostility, and even revenge toward males. This may appear as chronic nagging, depreciation, and shrewishness towards their partners. Such attitudes, obviously, will interfere with normal, satisfying, adult sexuality.

Adult sexuality thus depends on many factors — physical health is important. Experiences of childhood, adolescence, and adult life modify one's sex attitudes. Training is obviously important. If parents have been undemonstrative or overly modest, the children will often have difficulty in freely entering into normal, happy sex relations as adults. Or if fear, guilt, repulsiveness have been attached to sex by parents, these associations will carry over into adult sexuality as unconscious disinclinations, inhibitions, guilt, fear, or restraint in normal adult sex life. Hence, the importance of wholesome parental attitudes towards sex in the training of children. Other carry-overs or residuals from childhood which may modify sex adjustment in marriage are attitudes that have been developed towards curiosity, cleanliness, spontaneity, naturalness, manners, modesty, feelings, control, reasons for expecting punishment, expectation of danger, fear, guilt, repulsiveness, etc. Many of these factors are far more important in satisfactory marital and sexual adjustments than reason, intellect, or mere good will.

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## MARRIAGE COUNSELING

EMILY HARTSHORNE MUDD, M.S.W.

EDITOR'S NOTE—*The importance of Marriage Counseling is clear. The increase in the number of organizations offering help in these matters shows that there is a widespread need for such services. All physicians see many cases when symptoms do not subside as they should under the usual methods of treatment, when convalescents do not convalesce, when recovery from accidents or surgical procedures is unusually protracted for no obvious reason. Symptoms also seem to arise for no obvious cause. Physicians are aware that somehow or other emotional factors must be entering into the condition. Conflicts and tensions accompanying marriage and family life are common sources of emotional and physiological disturbances with which the physician is called upon to deal. Often his knowledge of psychology and sociology does not enable him to deal effectively with these problems, in addition to the time limitations. Fortunately there is an increasing group of workers with special knowledge and ability in dealing with the problems of interpersonal relationships, especially in marriage and the family. Practically, their work has helpfully supplemented that of physicians. There are, furthermore, many patients who are unable to discuss intimate and personal problems with many physicians, because of differences in temperament, but who can freely and profitably go over these matters with counselors whose knowledge, temperament, and training put such patients more at their ease. Many patients with marital problems who need expert help will not consult available psychiatrists because of the still all-too-persistent idea that psychiatrists treat only patients with mental disease.*

*Marriage and family counseling supplies a community need. The war is increasing the number of hasty marriages. Marital tensions are going to be increased after the war. There is need for trained people to tackle these problems and help with them. The knowledge that workers in the field have acquired is important, available, and should prove useful to physicians. Furthermore, observations on the process involved when one individual helps another psychologically are important for physicians. Doctors' accustomed ways of therapy are so definite, concrete, aggressive, and authoritarian they are often awkward, ineffective, and anything but subtle. Their efforts in this field are frequently self-defeating, because their knowledge and skill are limited.*

*The discussion under the section "Philosophy of Helping" should prove of great value to physicians who want to be more effective and avoid many pitfalls. While this review is, therefore, not primarily medical, it supplements data presented in the body of the CYCLOPEDIA, and presents information that is essential for the wide-awake physician, if he is going to handle effectively family and emotional complications of his patients, and be a leader in his community in helping to solve constructively many family and marital problems which the war is forcing on our communities.*



### What is Marriage Counseling?

"Effective counseling consists of a definitely constructive permissive relationship which allows the client to gain an understanding of himself to a degree which enables him to take positive steps in the light of his own orientation."<sup>1</sup> Marriage Counseling, then, is that part of counseling which deals with any aspect of marriage. The purpose of marriage counseling is to help in the prevention of, or alleviation of, marital maladjustment—to prevent the waste and frustration of energy. The tacitly understood, although seldom verbalized, goal is to aid in producing more constructive, more creative, and more stable family relationships.

### Organization of Marriage Counsels

The fact that marriage counseling exists today in any formalized and professionally recognized form may serve as an illustration of the so-called cultural lag. Advances in mechanization and in knowledge and new approaches in the physical and psychological sciences have increased at a greater speed than changes in social institutions, customs, and mores.<sup>2</sup> Therefore, human beings find themselves caught in a complicated world in which their activities are perforce carried on under conditions some of which were not even in existence when the rules and regulations governing their conduct—the social sanctions of state, church, and home—were evolved. As a result, many decisions in present-day behavior must be made largely by each individual by himself and for himself. Mistakes and conflicts, therefore, are inevitable. Marriage consultation services are interested in helping people learn to avoid or at least handle their conflicts. They have been formed in different ways in different communities according to the local need. This independence during the early phases of development is healthy and

enables each group to pass on to others the benefit of its experience.

**European Examples** — There were more than one thousand marriage consultation centers in Germany and Austria in 1932. These were "chiefly a post-war (World War I) development," writes Kopp.<sup>3</sup> "Although operating under a variety of names, they have the common purpose of directing public opinion toward the betterment of national health in relation to the family." This approach has been radically revised as a result of European political upheavals with their submergence of the individual in nationalism and race purity. World War II finds family counseling services, as we know them, only in the democracies where interest is preserved in aiding each citizen to grow and develop to his greatest capacity.<sup>4, 5</sup>

**When and How to Start a Counseling Service**—"In organizing a family or marriage consultation center," states Carden,<sup>6</sup> "it is vitally important to know whether there is a demand for counseling which is not being met, and whether the community is ready for a center. This information determines whether it is better in a particular community to attempt to organize a center or to interest an already existing agency in expanding its work, or whether for the time being, it is better to take no action at all." The location for a center determines to some extent the impression which the center makes and the type of individuals who avail themselves of its services. Tentative policies for a program should be set up before the center is opened. The educational work needs to be integrated with the counseling. Clients often come to a center with a preconceived idea as to what they will get from it. This idea, which has evolved from the way in which they have had the service interpreted to them, either helps

or hinders the counseling procedure. The individuals who are carrying on the educational and interpretative part of the program need to be oriented to the philosophy of counseling accepted by their service in order that they may present it in their contacts. The use of the library should be correlated also with the counseling procedure. Publicity and public relations should be coordinated with the whole program of the center on a sane basis with avoidance of the sensational.

There is something of a dilemma in attempting to start a family or marriage counseling center. People want to be sure of its value before giving it support and it has to have support in order to start. Unwarranted optimism about the future of such centers, due in part to the repeated statements that the movement is spreading rapidly, has caused groups of individuals to start services which they were not able to continue.

**Services of Recognized Community Position**—Many individual doctors,<sup>7, 8, 9</sup> social workers,<sup>10, 11</sup> ministers,<sup>12, 13</sup> lawyers, and teachers,<sup>14</sup> in addition to various professional groups, are taking definite interest in marriage counseling *per se*. The following quotations from an unpublished report of the special committee of the Family Welfare Association of America<sup>15</sup> indicate the thinking of one powerful group:

"... There is a growing interest on the part of social agencies in marriage counseling as it becomes evident that case work service is needed and wanted by groups in higher income levels. . . . The selection of personnel for this service is essential to a high standard of work, with a well-trained worker with five years' experience in general case work suggested, and experience in consultation with psychiatrists and psychoanalysts. . . . There seems to be a possibility of enrichment to the agency in such a service which is well interpreted and understood in the community. Some agencies have drawn into activity in the marriage counseling program, laymen, clergymen, lawyers, and doctors,

who are valuable in contributing knowledge and sharing interpretation."

There are many individuals already doing marriage counseling and approximately 25 agencies functioning in 12 states, all in urban areas. A few of these centers have been open for a sufficient length of time to enable them to contribute, on the basis of actual experience, to knowledge in this field.<sup>16, 17, 18, 19</sup>

An examination of leaflets describing and interpreting to the community the services now in existence is of interest. As space is not available to quote from every center, samples are chosen from different sections of the country.

In California we find the oldest service in the United States, *The American Institute of Family Relations*, in Los Angeles. This organization offers *Preparation for Marriage* through its "premarital service"; individualized counseling in *Marital Adjustment*; *Parent Education* to show "fathers and mothers how to deal with the everyday difficulties of their children"; *Public Education* through lectures, conferences, and discussion groups; and an *Extension Service* "to aid those who are called upon to lead, advise, or instruct others in dealing with their personal and family problems." This organization, directed since its inception by Dr. Paul Popenoe, is "incorporated by a group of California men and women as a nonprofit educational enterprise for public service." In a different part of this state *The Family Relations Center*, run by Mr. Henry Grant in San Francisco, functions.

In Ohio we find two active and very different types of services. *The Premarital Consultation Service of the Maternal Health Association of Cleveland*, directed by Miss Gladys Gaylord, "is offered to men and women who want advice and help in solving the normal problems of marriage." It is supported by private contributions and fees. *The Family Consultation Service in Cincinnati* is a department of the Associated Charities. Under Mrs. Anna Budd Ware it "offers advice and counsel concerning any family problem," and is paid for through Community Chest funds.

In Massachusetts *The Counseling Service*, "the first of its kind in New England," is offered in Boston by the Massachusetts Society for Social Hygiene in cooperation with the

Boston Y.M.C.A. under the directorship of Mr. Lester Dearborn "to any man or woman who needs expert advice and assistance towards solving the normal problems of marriage and everyday life." This service is supported by appropriations from the two sponsoring agencies which in turn are members of the Community Chest.

In Pennsylvania *Marriage Counsel of Philadelphia* "was established in 1932 to help young married couples and those contemplating marriage to a better understanding of what companionship in married life involves, and thus to help them avoid some of the causes of marital difficulties." It offers individual counseling, and, in 1943, a special premarital service which covers all state legal and health requirements; educational service through lectures, group work, and advisory conferences; a lending library and publications based on working experience. It is a nonprofit community agency supported by memberships and to a small degree by fees from services.

In North Carolina Dr. and Mrs. Ernest R. Groves at Chapel Hill offer through the *Marriage and Parenthood Consultation Service*, "to give counsel to those with personal marriage and parenthood problems."

In New York the *Marriage Consultation Center* in New York City at the Community Church, directed by Dr. Abraham Stone, "provides an advisory service for the married and those about to be married in marital hygiene and related topics." The *Bureau of Marriage Counsel and Sex Education*, also in New York City, offers, through Dr. Valeria Parker, "personal consultation on confidential problems relating to sex and marriage adjustments; lectures, youth forums, parent education, seminars, family relations institutes, and university, college, and teacher training courses."

It is obvious from the above examples that there is a definite general similarity in purpose, means of support, and emphasis on a so-called preventive approach in the centers cited, although the origin, backing, staff personnel, and methods of functioning may be varied.

**Who Counsels**—In these centers marriage counseling is primarily of a psychological nature and utilizes the concrete aids of medical examination, psychological testing, bibliotherapy, etc., only

in addition to the conference between counselor and client. Therefore, the personality, ability, and cooperative capacities of the staff in any center are of paramount importance.

Of the 36 counselors in the center studied by Carden<sup>6</sup> all had a good educational groundwork and the majority specialized training in some field. Seventeen had undergraduate college degrees plus extra courses. Eight had masters degrees, four were doctors of philosophy and eight doctors of medicine. It is of interest to note that in 1942 the American Association of Marriage Counselors was initiated and is now in the process of considering membership requirements.

The majority of the functioning counseling centers have several counselors with different training and backgrounds, each available on part time. A few offer to the professional individual a full-time salaried position with adequate year-to-year security. It seems probable that few of those now doing counseling planned their education to fit them for it. Rather, their counseling work probably developed because of their personality, attitudes, and experience. Obviously, the personal experience of marriage and parenthood gives a counselor more than academic knowledge of the experiences of his clients. Every counselor, however, must be aware continually of the limitation of any personal experience and of the danger of identifying problems presented by his clients with those which stir either his own anxieties, frustrations, or enthusiasms. A mixture of warmth and objectivity is a great asset.

**Who Sponsors**—The caliber and achievements of the men and women on a sponsoring board should place a marriage counsel in a position of unquestioned standing in the community in which it operates. The influence of such backing and the ever-present expert ad-

vice of clinical, educational, and other committees should both amplify and focus the training of the staff and serve as an increasing impetus toward critical evaluation of program and procedures.

**Interprofessional Relations**—Friendly and active working affiliations should be maintained with each of the main professional groups—with social work, with law, with medicine, with the church, and with education through staff teaching contacts in nearby schools and colleges.

**Research Possibilities**—Individual specialists, Burgess and Cottrell, contributed thoughtful investigations in family relationships. The editor of a well-known medical journal said ten years ago:

"The medical profession has been made to realize, perhaps too slowly, that there are allied fields with which its contacts have not always been sufficiently close. The study of marriage justly may be regarded as one in which the doctor assumes a responsibility and should manifest an interest equal to that of the sociologist, the psychologist, the lawyer, and the clergyman."

The National Committee on Maternal Health holds that "*cooperative research enterprise* must be maintained . . . to offer marriage counsel we must ascertain marital problems and their causes." In one project the author reports<sup>20</sup>: "Personality maladjustments were found to play a very significant rôle in causing or contributing to the development of complaints and problems in many of the obstetrical and gynecological patients. Personality maladjustments are the result of the woman's inability to make a satisfactory adjustment to disturbing physiological changes or illness, or to personal, interpersonal, social, and economic problems and difficulties. Physiologically, these anxieties and conflicts make themselves manifest by interfering with the usual functioning of the auto-

nomic nervous system and endocrine system. Disturbed functionings of these systems were responsible for the majority of the somatic symptoms and clinical disturbances in the patients studied, in whom no 'adequate' organic pathology could be discovered to explain either the intensity or multiplicity of the complaints. This concept is of great importance in the therapeutic management of these patients, for any treatment which was not directed toward an alleviation of the causes of the personality maladjustment was found to be disappointing to both patient and physician."

The following letter from a physician in a hospital endocrine clinic to a counselor in a marriage counseling center gives a concrete illustration:

"We continue our grateful recognition of the good work you have done for Mrs. X, and have suggested that she see you again. Her family problem is so large that it tends to absorb her attention at the expense of her physical condition. Of course, they are tightly entwined, but our clinic is not organized to handle emotional complications well, and the present shortage of physicians prevents our giving as much time as we ordinarily would try to extend to patients presenting emotional tangles. It would help if we could know that you are assisting Mrs. X in her marital adjustments."

According to Mowrer,<sup>21</sup> "the first function of counseling, obviously, is therapy; the second is research. The relationship between the patient and the counselor is the source of knowledge from which may come a more thorough understanding of personality and family problems."

Individual specialists have contributed thoughtful investigations in family relationships and human behavior.<sup>22</sup> Recently, the stimulating contributions of Weiss and English,<sup>23</sup> Levine,<sup>24</sup> and others emphasize the inescapable interrelationship of the emotions to disease as focused in the intimacy of family relationships.

Marriage counseling centers have within their client-counselor contacts, their case records, their interrelated and coordinated professional staffs and committees the possibility of contributing to the understanding of psychosomatic conditions and psychosocial relationships of human beings. They have begun to utilize, coordinate, and focus on questions relating to marriage the abilities and findings of the main fields of the biological, psychological, and social sciences.<sup>25</sup> The productive potentialities in cooperative research in marriage counseling centers are as yet largely unexplored.

### Who Are Counseled

**The Counselees**—The following distribution of intake is probably fairly typical of most marriage counsels:

During 1943, nearly one-half of the clients were engaged couples. They represent a cross section of the community, more women than men, representatives of all religious groups. More *young* married couples come than formerly, the predominant age group being between 21 and 30. Over two-thirds of these clients paid a modest service fee from 25¢ to \$5, an average of about \$2 per paying client. On this basis, fees can be only a nominal source of support, although a definite help in establishing a self-respecting, dignified, give as well as take, relationship between the client and the counsel. No client is ever refused because of established inability to pay any fee. More than one-half of the clients had one interview, the rest two, three, four, and a few five or more. Most of these clients had further contact with the service by phone, letter, or through the use of the lending library.

It is obvious from the numbers of short contact cases that marriage counsels have the opportunity of helping other organizations in the evaluation of short contact work.<sup>41, 42</sup>

**Evaluation of Service** — Reports, such as the two quoted below, are now beginning to be available to furnish some estimation of results in a few of the family counseling organizations:

"The Institute is particularly proud of its Premarital Service, which is offered to those about to wed who want help in making their marriage a success. . . . That the Institute's service provides what they want is evidenced by the hearty appreciation which they have expressed.<sup>17</sup>

"On February 3, 1944, the Institute began its fifteenth year of work. The past year has shown a continuation of the organization's steady growth. Intensive counseling was given to 1088 persons, while the educational activities of the Institute were expanded widely in spite of wartime difficulties."

"The purpose which, ten years ago, prompted a handful of men and women working in different professional fields to open Marriage Counsel of Philadelphia, although reconsidered each year, has remained basically unchanged. The results of work in this organization have proved the validity of this original concept. Each year approximately one-half of the clients have been engaged couples; and only a negligible group have come after their marriage has reached the breaking point. Follow-up reports indicate that service received has, in many instances, helped toward the establishment and continuation of constructive homes and happier family life."<sup>16</sup>

### A Therapeutic Approach

**The Process of Helping** — Social work has arrived at the stage of experience in which the more creative members of this profession have contributed critical interpretations and evaluation of some of the processes which take place in interviewing.<sup>26, 27, 28</sup> Progressive psychiatrists have amplified such thinking.<sup>29, 30</sup> That reference material on this subject is available in the literature is of great practical assistance to students in training and marks an important point in the growth of the social and psychological sciences. One marriage counseling center has formulated its approach to clients in a study on premarital counseling.

"We have assumed that the major benefit from such a service as ours is derived from those unspoken but deeply felt reactions which may occur at the meeting of two individuals. A young person who makes up his or her mind to seek

outside help from a marriage counsel has proved to himself that he really wants to do something about his situation. This is an emotional experience which brings confidence to the client, and an intensified participation in the actual interview, and which constitutes the most important step in his ability to make use of the service.

"The client can then feel that . . . there is another individual who has lived through the same experience that he himself is about to face, and who gives reassurance and understanding. This unspoken, but deeply felt, interchange may be responsible in great measure for the finding, borne out by seven years of work, that so much seems so often to happen in only one or two interviews.

"Change, in our experience, can occur only when the client himself has a sincere desire for help. The attitude of mind of those few who come *only* because they have been urged to do so by some well-meaning friend or professional person renders an interview of little value to them. Even though the counselor may be cognizant of many problems, discussion of them is usually academic and sterile, without a sense of actual participation on the client's part."

**A Philosophy of Helping** — The philosophy with which the staff of one marriage counsel has carried on its work grew through the belief in the dynamics of human relationships—the meaningfulness of one human being to another. This philosophy holds that everyone has a right to available knowledge; that most people, if accepted as they actually are, without condemnation or manipulation, will respond to naturalness, understanding, and warmth. Through the relief of being themselves, of having up-to-date information available, of understanding something of the basic motivations of personality development, they can then go on to the utilization of the innate strength inherent in some degree in everyone. By a change of attitude, they become able to survive and even live creatively within the same framework that existed when they first sought help, or find the courage and initiative to effect a difference in their surroundings by

*their own efforts.*<sup>16</sup> "In dealing with the inner life of man it becomes possible for him to handle the outer and material realities to which he is related."

**An Ounce of Prevention**—Findings in a marriage counsel office are perhaps suggestive for the future. The records of 100 consecutive men and 100 consecutive women studied showed a positive correlation between the amount of education which these individuals had received and the use they made of a marriage counsel. In other words, the great majority of men and women with high school or less than high school education came to the marriage counsel *after* marriage and *after* definite problems had arisen. The majority of men and women with high school, college, and graduate education came to the marriage counsel *before* marriage in an attempt to prepare themselves as well as possible to make a success of their new venture.

These facts become more significant when the records of these clients were analyzed further to see how many of the 103 clients who came before marriage reappeared later with problem situations sufficiently intense to lead them to seek further help. Although over 73 of this group were heard from later, *nine only* reported difficulty in adjustment and came for further help.

**Everyday Guides for the Married Couple**—"Every married couple," writes a counselor, "should understand or have access to information on the following relationships which are most often involved in the problems of marital adjustment as well as in personal peace of mind:

"1. The elementary anatomy and biology of the reproductive organs should be understood. Just as one is a better driver of an automobile if its mechanical principles are understood, so will one be in better control of the self if human biology is comprehended.



"2. The possible variations in feminine interests, desires, and physical reactions in relation to the menstrual cycle are manifold, but observation and allowance by both the husband and wife can add to marital happiness.

"3. The psychology of sex satisfaction grows out of the biology of the male and female. A normally developed woman has the possibilities of satisfying her sexual capacity just as much as a normally developed man. Women usually require a combination of tenderness and sensuality before they can give themselves completely in the love relationship. Men require less tenderness and are more direct in their reactions and, therefore, sometimes find it hard to understand and complete their wife's needs.

"4. Most couples find pleasure in learning to meet and satisfy each other's needs and desires. Many couples find pleasure in experimentation and variety in their mutual love relationships. There is no one correct way of love; rather, many couples find that love grows on subtle change and variety.

"5. Simultaneous satisfaction is not always possible and even those who have achieved it may not experience it at all times. A couple who have worked out a mutually satisfying and happy method of sexual expression usually find that it grows out of their unity and can be a cornerstone of vital importance to happiness in marriage.

"6. The married couple should remember that a holiday spirit of relaxation, spontaneity, and wholehearted enjoyment, and, in addition, plenty of time, fastidious personal cleanliness, and attractive and private surroundings all act as favorable influences in sexual adjustment. By the same token, continuous mental, nervous, or physical fatigue, or carelessness in personal hygiene of one or both partners can account for many difficulties, dissatisfactions, and frustrations.

"7. Adequate spacing of children may be advisable for the health of any woman. Therefore, the use of some natural or mechanical method of family limitation may be important. Every woman should feel free to ask her family physician or obstetrician for this information.

"8. The sexual relationship in marriage seldom continues to be satisfying to both partners if either partner has consciously or unconsciously dominated the other through coercion or through possessiveness. Marital happiness is not a question of either wholly give or take, but rather of emotional compromises gladly made since they add to mutual affection.

"9. Most marriages can be successful if both partners employ the necessary time, thought, and good will to make this possible. Usually, the depth of affection, understanding, and appreciation increases with the years together. If, however, the personalities or previous attitudes and values of the pair lead to continuing frustration and strife, separation should be seriously considered. Evidence shows that children reared in a home of severe conflict are more apt to acquire personality difficulties than are children raised in a broken home where the affection and security of one parent are assured.

"10. Sexual expression is only one part of life and marriage but it is, with the exception of a few marriages, of fundamental importance and, when shared with a beloved partner, contributes vitally to the positive emotions—the humanizing, sharing, creative, and spiritual forces in life."

**Everyday Essentials for the Counselor**—In addition to the above subjects which seem to be involved most often in marital adjustment, the following are suggested as "essentials of counseling" for a premarital interview:

1. The importance of individualizing the premarital interview—taking the person where he or she is, and going on from there.

2. The importance of asking the client a few simple questions, the answers to which will indicate the client's *attitudes* toward the physical and emotional adjustments involved in marriage.

3. Discussion of these attitudes by the counselor, and through this discussion, the giving of information which is desired or for which need is indicated.

4. Recognition by the counselor of the naturalness of the apprehension or fear apparent in many individuals as they approach life's most intimate, and, for them, as yet unexperienced relationship.

5. Recognition by the counselor that some masturbatory and occasional homosexual experience during the premarriage years is common to the great majority of men and women, and does not interfere with a satisfactory sexual adjustment in marriage, unless the indi-



vidual involved has lost interest in the usual forms of heterosexual expression, or has become overly apprehensive about his chances for adjustment. Such a reaction would probably be due largely to the guilt and fear incurred as a result of the outmoded moral attitudes of society rather than to the experiences themselves.

6. Realization by the counselor that the opportunity to talk out the way one feels about things is probably more important to the client than covering any prescribed amount of information. Reading can give supplementary information if there is not time to cover all facts during the interview.<sup>31</sup>

7. Reassurance by the counselor that learning to live together closely, both physically (sexually) and emotionally, requires time and patience, and almost always involves incidents which are disappointing and unsatisfactory for one or both partners. This does not mean failure, but indicates opportunity for improvement. "Where there is a will, there is a way." The "ideal" often develops only as mutual knowledge, understanding, and confidence between the partners increase with experience.

**Group Education**—Access for individuals to expert professional skills is going to become increasingly difficult in the immediate years ahead. Many people during the war will solve or escape their problems temporarily in activity. Others will perforce have to work out some of their difficulties through the use of written material,<sup>32, 33, 34, 35, 36</sup> radio and group education.<sup>37</sup> The possibilities within these approaches for the field of *premarital* education and *postmarital* adjustment are fascinating and have applicability for governmental agencies as well as for private resources. Through analyzing the work of marriage counsels we have become familiar with the univer-

sality of certain individual emotional reactions within our cultural heritage. It is because of this experience that marriage counseling may now hope to contribute to the exigencies of the times.<sup>38</sup>

### War Repercussions

Inevitably the strains and stresses of a world at war will be reflected in the emotional reactions of those individuals who are caught up in the relentless grinding of this impersonal machine. Families often will be affected deeply.<sup>39, 40, 41</sup>

"Due to the upsetting social and economic conditions resulting from the present war emergency," states Dr. Gardiner, "we can anticipate the appearance of many personal and interpersonal anxieties, problems, responsibilities, and catastrophes to which it will be most difficult, and in some cases impossible, for women to make a satisfactory adjustment. . . . Obstetricians and gynecologists will do well to investigate the problems, responsibilities, and sorrows caused by the present war emergency in those obstetrical and gynecological patients among whom the physical examination does not reveal an adequate cause for the patient's symptoms. By keeping these possibilities in mind, much needless medical, endocrine and surgical therapy will be avoided."<sup>20</sup>

Popular articles,<sup>42, 43</sup> based on the work of marriage counsels, give a glimpse which can be repeated in any counseling office of the multiple paths by which this war of ours bores its way inescapably into "the inner life." Both popularized and technical articles indicate opportunity for the Red Cross Home Service, the United Service Organization, personnel workers in defense industries, and other war workers to call upon the experience and service of marriage counselors.

Since Pearl Harbor there have been many more difficulties of adjustment among young married couples (often evidenced by sexual inadequacy) and fewer premarital conferences. Time is often not granted to proceed in a considered and orderly fashion. There is a compul-

sive *must* about achieving overnight the mutual understanding and ecstasy which naturally should develop in the peace and serenity of the innumerable days and nights ahead. This very tenseness and pressure all too often prohibit the achievement so ardently desired. Separation adds its suffering and conflicts before mutual adjustment has been achieved, and bewildered young wives and disappointed young husbands are the result.

The marriage rate increases in the beginning of a war period. In the United States, it reached its peak in 1941. The largest crop of babies ever to be born in this country arrived in 1942. Divorce is predicted in one-third to one-half of marriages as an aftermath of war.<sup>44</sup>

### Basic Human Needs

The reactions to these war strains and stresses and deprivations seem, for the most part, to have a fairly natural and logical relationship to the basic underlying needs of men and women. It is impossible to put in simple terms anything as complex as the motivating drives of human nature. However, within these limitations and with the perspective gained from the kind of problems presented by clients of marriage counseling centers and the ways in which counselors have seen these clients make use of such services and go on by themselves, we believe that "satisfying life is full of companionship, affection, and the need for response, recognition, new experience, and security." Such living involves the sharing of experiences with others.

When an individual, as he or she develops, is deprived of too many of these needs, he becomes frustrated or warped in some way. Anxieties, fears, aggressions, hates, the need to dominate others—negative forces may become overdeveloped. These forces next become apparent in behavior which brings unhappiness

and dissatisfactions either to the individual himself or to those others most closely associated with him. As marriage is admittedly the most intimate of all interpersonal relationships, it seems natural then that the actual conditions of marriage should bring to a focus individual reactions which take form in various types of behavior. When these emotions are of a warm, positive sort, the personality expands and, as those who have discovered the depths of love know, life and the world are completely different. When the marriage relationship deprives the individual further of his needs for affection, recognition, new experience and security, symptoms of maladjustment are apt to occur and help is needed and sometimes sought.

Young Mrs. X had been married only one and a half years. When her husband was drafted into the Navy, he told her, as he was leaving, that he was not satisfied with their marriage and thought they should break up. Completely surprised and terribly shocked, Mrs. X was left alone. She told the counselor, "I knew there must be some place in this city where I could get help." The telephone listing had led her to a marriage counsel.

During a series of interviews with a counselor, Mrs. X was able to discuss her attitude toward her marriage and to talk over some upsetting experiences, never before mentioned to anyone, which had happened to her during her adolescence and young womanhood. These discussions helped Mrs. X to gain some understanding of the normalcy and importance of giving and sharing and enjoying physical as well as other types of companionship in marriage. She realized for the first time the needs of a healthy young husband. In addition, reliable factual information plus medical examinations and help suggested by the counselor enabled Mrs. X, through her change of attitudes, to relate her self warmly and positively to her marriage. Her husband so appreciated the change in his wife that gradually his love for her was reawakened.

A letter from Mrs. X tells the results: "I know the enclosed money can never repay you for all you did for me, but it might aid a little in your continuing your work and thereby help some other young couple that are facing the

same problems Bill and I did. . . . Things are just going along wonderfully now, and I think we are more in love than we ever were."

## Marriage Counsels and the Changing World

**The Present Situation**—The world is changing and social institutions will change. If change in education and social institutions was abreast of the change in the physical sciences and mechanization, there would be insistence on revising the requirements and forms of society to meet more realistically the basic motivating needs of human nature as it must function in our present environment. If this revision were in effect, marriage counseling, in all probability, would be as unnecessary as it has been in the Samoan Islands. Change is sometimes uncomfortable but sometimes to be welcomed. That which is unique and which has a contribution needed by the times will survive—if not in the form with which we are now familiar, then it will be utilized in other processes through the technics, the findings, and the spirit which it has engendered.

**Prognosis**—Steinbeck's hero, Mayor Orden, emphasized the essentialness of people understanding each other. "In all the world," he says, "yours is the only government and people with a record of defeat after defeat for centuries and every time because you did not understand people."<sup>45</sup>

Marriage counsels are equipped to help people to understand themselves and each other in family relationships, and to realize and utilize their constructive abilities and their strength. It can be expected that in so doing a foundation will be laid toward more positive human and world relationships.

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## JUVENILE DELINQUENCY IN WARTIME

G. HENRY KATZ, M.D.

**Definition**—We are hearing a crescendo of warnings that delinquency is increasing alarmingly among children during this war period. Legal and social agencies, educators, doctors, writers, commentators tell us that our fortress is not only stormed from without, but is also threatened from within by our own children by reason of growing juvenile delinquency.

Juvenile delinquency was defined by the White House Conference of Delinquency as "any such juvenile misconduct as must be dealt with under the law." Freed of the legalistic interpretation, it is a conflict of the child with his social milieu great enough to call forth protective and corrective measures. Obviously, this includes vast differences in the nature and extent of the offenses, depending on the mores of the community. The son of a Filipino Moro chieftain might be delinquent if he failed to take the head of an enemy killed in battle; the son of a middle-class American family might be considered delinquent if he cut school frequently. Those who offend through ignorance, feeble-mindedness, or

psychosis are not included. Nor are those whose delinquent activities are preponderantly self-defeating rather than injurious to the rights or property of others, such as many alcoholics.

### Is Juvenile Delinquency Increasing?

The Municipal Court of Philadelphia in its 1942 report states: "The number of cases of children under 18 years of age increased 16 per cent in 1942 as compared with 1940. Boys' cases increased 9 per cent; girls' cases increased 54 per cent. One significant effect of the changes in family life and living conditions which have taken place in this city during the past two years of preparation for war and actual war has been an increase of 83 per cent in the number of delinquent girls under 16 years of age; 391 cases in 1940 and 715 cases in 1942." For the first ten months of 1943, according to the *New York Times* of April 7, 1943, the Children's Division of the Domestic Relations Court of New York City had 871 white and 419 negro boys' cases, while in 1941, the comparable cases were 689 and 248 respectively. On a broader field

it is stated: "An increase in cases disposed of from 1940 to 1941 was reported by 22 courts, and a decrease by eight courts. Similar increases were seen when the 1941 figures were compared with the 1939 figures; 21 courts reported an increase and eight a decrease (one court did not report for 1939). In the 22 courts that reported an increase from 1940 to 1941, the per cent of increase ranged from 2 to 110. In 11 of the courts the per cent of increase was 20 or more."<sup>1</sup>

Glueck<sup>2</sup> says: "The impact of the war upon our society has created a multiplicity of problems which the nation must solve if it is not to have a terrible aftermath of chaotic years. The delinquency among adolescents brought on by the war is a major problem. Since the advent of war there has been a tremendous increase in juvenile crime. In certain sections of the country, the aspects of a crime wave are present. For example, the increase in crimes among youths ranges from 2 to 110 per cent over an equal period last year. There may be other factors contributing to this rise, but the most important factor is the war itself."

Mr. J. Edgar Hoover has repeatedly warned the country about the dangerous increase in juvenile crime.

Before accepting the conclusion these figures and statements indicate, other factors which may qualify them should be considered. Numerous as the reports are, they touch on only a small proportion of the total population and even so are probably not immune to influence by emotional reaction.

The war has brought a considerable shift of population from scattered to concentrated habitats, from farms and smaller communities to cities, so that the total number of potential delinquents who come under the view of fact-finding agencies is increased. Children coming

from sparsely settled districts where greater individual freedom is possible without impinging on others' rights must have time, training, and experience before they know what is expected of them and learn new ways of living and expressing their spirits which are acceptable in their changed surroundings. Exciting new contacts with other children and the accompanying incitement to be daring lead them into conflict with the more compact organization of the city. Current statistics show there is a decrease in delinquency cases in rural areas, although the total decrease is much less than the increase in the cities.

It is possible, too, that parents and others now are calling on the courts and agencies with greater frequency than formerly. When so many parents are away from home much of the time in war work, many of them will want more discipline than they themselves can supply. This is particularly applicable to families coming from rural districts whose older generations view with alarm many of the activities of city life which the younger generation finds so alluring. With lessened supervision from the home, children will surely get into more mischief. Many of the local population are fearful of or inimical to newcomers and call the authorities for offenses they would tolerate from older residents.

Changing moral codes may be a cause for more children getting into trouble. Excitement over the evils of youth repeats in and out of wartime since time immemorial. Since there is no fixed standard for morality measurement, we can only use our judgment as best we can.

For clarification of the problem, we turn to other wartime experiences. Our own country was in the last war too briefly, and available data are too vague to be of help. However, Professor Moritz

Leipmann published a report showing convictions of boys in Germany in 1913 were 46,000, while in 1918 they had risen to 85,000. For girls, the comparable figures were 8000 and 14,700. Interestingly, sex delinquencies among girls in Germany declined greatly in that period, while their great increase here at present is a major concern. Professor Leipmann noted the great importance of broken homes in accounting for the shocking rise, of removal of the parents and older children from the home, of increase in child labor, and of the earnings of children, and undernourishment, all of which decreased home influence and ties. The effect of schools in restraining and guiding the children became greatly vitiated. Drafting of the teachers, lack of fuel, use of schools for other purposes, and use of the children in other and more intriguing activities than study, encouraged truancy and reduced the schools' efficiency.

Glueck,<sup>2</sup> in her study of children's delinquency in England during the present war, reports an increase of about 63 per cent due largely to subnormal children, in whom it rose 600 per cent. A decrease of 23 per cent was noted among the normal children. Bad or substandard familial conditions would appear to be the most important factor as few well cared for defectives were offenders. Broken homes, poor housing, lack of recreational facilities, long hours in overcrowded shelters, are all contributing factors.

While in this country the delinquency figures have increased and decreased at various times in the recent years in which statistics were in comparable forms, it is difficult to believe that the increase in only two years since the war began, several times that ever noted before, is not largely due to the influence of the war itself, as was apparent in the case of Germany during World War I

and is seen in England during the present war.

### Why Does Delinquency Increase in Wartime?

Students of juvenile delinquency in peace have stressed with remarkable unanimity the importance of poor home conditions as a prime cause. In *One Thousand Juvenile Delinquents*, Sheldon and Eleanor Glueck state that 41.8 per cent were living in homes which "had been broken by the death, desertion, divorce, separation, or prolonged absence of one or both parents. . . . Half the thousand boys had been taken from their parental homes at one time or another prior to their appearance before the Court." Other statistical studies show comparable figures. Mr. J. Edgar Hoover says in *The Youth Problem of Crime*, "We have youth crime because we have failed to provide them with proper adults and upbringing."

Poverty contributes greatly to poor home conditions. The families of the *One Thousand Juvenile Delinquents* were on the "lowest rung of the socioeconomic ladder; for, even in a period of normal employment, 68 per cent of them hovered precariously on the margin between self-support and dependency. . . ." The schooling of the parents was found to be remarkably low with no formal education whatsoever for one or both of the parents in 50 per cent of the cases. The parents of a very large percentage of the juvenile delinquents have been born in foreign countries. Shaw and McKay's study shows a very high incidence of delinquency in "blighted areas," in some of which areas the rate is beyond 30 per cent and diminishes fairly regularly toward the better residential areas. Blighted areas are usually close to large industrial centers.

Delinquency is largely a shared activity and the part played by gangs is considerable.

Feeble-mindedness, which is so significantly linked with increased crime by children in England during World War II, has not been an important factor among delinquents in this country, where it has not exceeded 10 per cent. Border-line mental disease and mental deficiency are computed as another 10 per cent. Only 2 per cent of the criminals in penitentiaries are found to be psychotic.

During war, poverty decreases, at least until such a time as universal scarcity brings about want. But many families have left their usual surroundings and are living in crowded conditions and in the midst of squalor which cannot be corrected because of housing conditions, in spite of the parents' good wages. The other peacetime factors that have been shown to have relation to delinquency are not remarkably changed with the exception of the home. In a great many cases, both parents are away much of the time and the children are thrown on their own resources.

Other conditions which influenced the creation of delinquency in Germany in the last war, and many of those which are influential in England during World War II, are present here, such as overcrowding and understaffing of schools in the industrial areas, the increase in child labor and in the independence of the children who are working, the lack of healthy outlets for excess energy.

But, in spite of the conviction carried by gross figures and total numbers, the understanding of delinquency is very incomplete. Some investigators have even gone so far as to say, "There is no scientific knowledge in the field of criminology. We have no knowledge of the causes of criminal behavior or of the effects of different modes and varieties

of treatment upon actual or potential offenders or of the efficacy of programs and measures of prevention.

"In the absence of such knowledge, we are and will continue to be impotent to control criminal behavior. . . . The knowledge which has resulted from criminological research is knowledge descriptive of the characteristics of criminals and of their environment.

"This descriptive knowledge has little utility in the solution of the practical problem of controlling criminal behavior, either through programs of prevention or through the official treatment of offenders. . . . It can be employed only in trial-and-error attempts to control criminal behavior and therefore has little practical value."

### Psychology of Delinquency

The answers will eventually be found through accumulation of microscopic studies of the individual to add to the macroscopic studies of the large group. Just as the understanding of neurosis comes from an understanding of the individual neurotic, so greater understanding of delinquency can come from the study of the individual delinquent. Such a study must be from the standpoint of deep or unconscious psychology to be productive because, while most delinquency frequently differs from neurosis in that it is volitional, the delinquent is no more able than his neurotic brother to explain why he differs from the normal, why his coveting or resentment or callousness are greater than those of the nondelinquent. Unfortunately, delinquency does not lend itself so readily to psychoanalytic investigation as does neurosis since the delinquent is not usually spurred on to treatment by inner conflict and anxiety. Like the paranoiac, most delinquents ascribe their delinquency entirely to incitement by the



outer world which they mistrust and so can conceive of no gain to be attained by ceasing to fight the world and attempting instead to change themselves and their reactions. This is not invariably the case. Another obstacle in the way of increasing understanding of the delinquent through deep psychological studies is the financial one. Many hours of the analyzing physician's time are required to gain insight into even one case, and the money to finance such studies, not for one cases but for the many cases required, is not generally available.

In spite of these difficulties, beginnings have been made. Some delinquencies arise from neurotic causes and these special ones lend themselves more readily to analysis and have come to be understood—those in whom the child has become identified with a parent whose moral standards are faulty, those who are delinquent because they are seeking a surcease for guilt through securing punishment, and still others whose delinquent actions take the place of the neurotic symptoms in neurotics.

There has always been a disturbance in the early affectionate relationships of nonneurotic delinquents the writer has known, resulting in the child's feeling he had been deprived of affection, so that he became angry and jealous in consequence. In some instances, the child had really been unloved. In others, he had had an early excess of intimate affection lavished upon him and the more formal relation as he became older seemed coldness to him. In any case, the delinquent feels, consciously or unconsciously, that he has been treated unfairly in this respect: Someone else has received what should have been his. Jealousy plays a large part in the delinquent's reactions.

Parents are gods to the small child. He has no conception of any forces greater than those of his parents. Thus, all good and evil that come to him he ascribes to his parents. Whenever conditions are such that he suffers, physically or emotionally, whether through their neglect or in spite of their greatest efforts to the contrary, he feels it is through their volition, and would have been different had they loved him enough to care. When a parent leaves for a considerable time, whether it is desertion or because of divorce or separation, or work's necessities, deep in the child's mind is the idea that he has been deserted in favor of another and this idea is overcome only slowly, if ever, by the realities of the situation. When the child feels he has been discriminated against, his need for regard and love has been frustrated. Although his ideals may be perfectly normal, he feels justified in taking revenge and can act without conscience scruples. Normal ideals can even enter the service of an attempt to enforce justice for himself: It is right for him to fight for such a cause and to take revenge. The concept that he is dealing with an adversary vastly stronger and more able than himself, the parent or the parent-surrogate, society, causes the delinquent to use whatever guile and trickery he can so as to get revenge without getting further punishment. Scrupulously fair treatment can help to still this jealousy of the delinquent.

He seeks to gratify impulses other than those of vengeance as they arise, also, with small thought of consequences, as though the ordinary considerations of prudence do not concern him. The normal child learns increasingly that his total welfare is best served by checking the pleasure gained through promptly expressing every impulse against the pain of the repercussions it arouses. His

keener knowledge of reality enables him to grasp this more readily than the child with less appreciation of reality. In order to gain this knowledge, all children need the control of an experienced guiding hand and the younger the child, the greater the need. To be on their own responsibility too much is to put them at the mercy of impulses which are not in keeping with our complicated social structure. For any given age the delinquent, the feeble-minded, and the neurotic need greater control than the normal. Too little control, too much "running wild" leads to increased crime.

Gangs especially need supervision and constructive adult direction if they are not to lead to mischief.

The delinquent is more cruel than others, either through lack of concern for their suffering or because of actual enjoyment of it. There is gratification in the hurts of others and delinquents veer toward those in whom, as Sigmund Freud said, "The sadistic component was able for constitutional reasons to develop prematurely and in isolation." All of us have this component in some degree. In wartime it comes to the surface quite openly, directed against the enemy. This and other of the underlying more primitive trends are seen more clearly as the ordinary veneer of civilization becomes thinned out under the impact of war. The child senses and sees the underlying passions more clearly. Aggression, hostility, and cruelty are loose in the world. The naked, primitive drives of man come clearly into view for the child to incorporate into his own code of feeling and action. He absorbs this civilization-denuding atmosphere and because his own veneer is in the process of being laid down and is less hardened and resistant, he sheds it more quickly and easily. Wartime letdown in adult morality infects children seriously.

A group of children, like a group of adults, tends to come largely under the domination of one person. That person is the one who possesses initiative and is willing to take the responsibility for the action of the group. Daring and initiative in children are largely associated with predatory activities involving defiance of the adult world. When adults, as members of a gang or mob, can put aside their lifelong individual ideals to embrace unquestioningly, for the time being those of a strong leader, it can be understood how much more readily this can occur in children whose ideals are still fluid and vague. Love for parents and surrogates and the wish to retain their parents' love themselves, again are the sources of the forces which tend to neutralize the harmful influence of the gang. The innate desire for immediate gratification is restrained because only by so doing is it possible for man to gain the benefits of group living. Satisfaction of a purely selfish nature is modified to include benefits to others as well as himself in exchange for similar benefits derived from them. But this arrangement is tenuous and, when disturbed, tends to swing back to the original narrow view. The baby starts out in life knowing only himself and interested only in his own welfare. Soon he recognizes his mother and learns that his welfare is tied up with hers. He identifies her welfare to an extent with his own and he fights for her as well as for himself. He further expands to take in others—his father, his siblings, his friends, his countrymen, all mankind if he develops so far. His concept of what interferes with his welfare changes gradually from persons immediately about him to strangers, from strangers to forces and obstacles of nature to be overcome. But arrayed against this expanding tendency is a reverse pull back toward the

narrow and primitive. Let danger increase, cupidity be aroused or ideals change and this regressive force becomes the stronger. The latest acquirements of civilization slough off the most readily, and nation flies at nation almost with relief at no longer having to maintain lofty altruism toward all mankind. There is great satisfaction in having a personalized devil to fight. And the more definite and better known the enemy, the greater the satisfaction, so the tendency is not to stop after the first step but to regress further and further backward along the path traversed in the individual's development which is that of civilization as well.

### **The Importance of Juvenile Delinquency**

Delinquency in children has import far beyond the trouble caused by the child's immediate actions.

Wood and Waite<sup>3</sup> state, "Information on the extent of recidivism among prisoners is of importance as indicating the extent to which criminal habits had become fixed." In the Gluecks' study of 500 criminal careers, over four-fifths of the reformatory group they studied had been arrested for offenses previous to the last. If the child has once been naughty in a certain way, he is much more apt than not to continue to follow that channel; that is, once an instinct has found a means of expression through action, there is a very strong tendency, even a compulsion, to repeat. The impulse of the child is like an internal rising emotional tension demanding quick action of the most direct type so that the pressure may be relieved and peace regained. Once the child has found a means of relieving this tension, he clings to it with great stubbornness and he is swerved from it only by long and arduous struggle. Delinquent action is a

direct outlet for such tension so that once established, the attenuated relief of less direct expression meets strong resistance.

The importance is obvious. It is far easier to train and control the child and his environment to avoid the committing of crime than it is to reform him afterward.

### **What Shall Be Done About Juvenile Delinquency?**

Obviously, delinquency is not a problem that can be solved easily by a single formula. In this, it does not differ from most other human problems, however, and because we cannot have a Utopia, we do not scorn those steps in the direction of amelioration that we can see and take at the present time.

To deal with the problem purely in accordance with the moral sense provides a special satisfaction. Society recognizes the element of spite in the delinquent and responds in kind, with a desire to punish rather than to treat the delinquent as a mentally sick individual. Even many kindly people feel an extremity of anger that is out of proportion to the offense committed. The idea "spare the rod and spoil the child" has wide appeal. It is a beautiful simplification. It is in accord with the sense of justice. Each of us has attained what civilization we have through struggle, through ruthless denial of the same kinds of gratification we see the delinquent obtaining, and it is natural for us to apply the repressive methods we had to use on ourselves, intensified, to others. But in following this school of thought we are really gratifying our own "good" sadistic trends, released under the very guise of idealism as a deterrent for the "evil" sadistic drives of others. It is necessary that in this field, too, we again take up the weary load of civilization,

put aside our own revenge impulses and approach the problem from the rational standpoint. Society's old answer to delinquency, punishment, has failed.

It has been seen that delinquency in the child begins in the effect on the child of the personality and character of the parents. As the child's horizon expands, other circumstances and contacts contribute toward conformity or delinquency, according to whether they strengthen or repel warm human ties:

(1) The safety and happiness of the child in the family circle, which is partly dependent on the economic circumstances of the family and the relationships of the parents to each other. Everything which tends to weaken the bond and the mutual respect between home and child increases delinquency.

(2) Those extensions of home influences, the school, with its teachers and companions, and the customs and reactions of those in the neighborhood and the community in which the child happens to have his home; the presence or absence of healthy outlets for youthful energies. Labor is not healthful for children.

War, disrupting many of the institutions that provide the child with security, and accompanied by massive regression of ideals, cannot be carried on without increased delinquency. The problem of delinquency has its roots in individual psychology as influenced by our entire social system. Solution involves continuous expansion of our knowledge of psychology and our changing of the environment to accord with this knowledge.

"The best rewards of therapeutic efforts are from working with youth." The smaller the child, the more plastic he is and the more at the mercy of his primitive drives. Hence, it is more necessary that these be met with kindly realism so that he may absorb this realism as a

means of his own expression. This situation with respect to delinquency is the same as with neurosis. The best place to prevent delinquency is in the home, the best time is during infancy. Fathers of young children ought to be spared to their families during wartime so long as it is possible to do so. Mothers are even more important. When, in total war, the time comes when both fathers and mothers must go to Army and factory, nursery schools, kindergartens and schools should supplement the home even to the extent of becoming foster homes, as Freud and Burlingham<sup>4</sup> have suggested with reference to nurseries. Although inferior to the home in many ways, much would be saved and even something gained.

Social agencies' activities should be enlarged during war, and their scope increased to provide more supervised play and entertainment for our young people—a United Service Organization for those not held closely by home ties.

The physicians, the child guidance clinics, the family societies, have a greater part to play in wartime than in peace in preventing delinquency through disseminating information and advising communities, parents, and children.

When delinquent traits have made their appearance, attention first is directed toward improving the young delinquent's environment so far as possible, not forgetting that most important portion of the environment, the human element. This is partly immediate, involving psychiatric advice and guidance for parents, teachers, courts, and others in close contact with the child, and is partly a long-time program, involving all the things which affect the human spirit.

When delinquency is established, direct treatment of the delinquent becomes necessary.

So long as the delinquent child can gain the gratification that comes from "acting out" his antisocial impulses, inner tension is dissipated. When acting out is frustrated, this tension, or anxiety, pushes vigorously for expression. A new, more constructive mode of expression offered then, has some chance of acceptance. It is like a mother saying to the baby, "No, you cannot play in the mud, but you may use this plastic clay."

Since acting out occurs in the emotional sense as well as in the field of action, it is important that the restraint be accomplished in such manner that resentment is not so great the child will be too angry to accept the substitutes offered. The methods of mental hospitals apply here perfectly: The patient meets with no more restraint than is necessary to prevent him from harming himself or others and this is offered in such a way that it is clear it is for his own welfare as well as others'. When this cannot be accomplished through home and school because the nature of the child's activities is too offensive or because of limitations of the personnel involved, a special residential school is most worth while from every standpoint—not the old "reform" school with its concept of reform through punishment nor the emotional reverse of this, one ruled by sentiment, but one proceeding along the lines already laid out by our juvenile courts and their co-workers, employing the best that science now has to offer and can further discover through Medicine, Psychiatry, and Psychology, Sociology, Penology, and Pedagogy to change personal and social liabilities into assets.

In such a school not only are the delinquent activities prevented, while other interesting and exciting activities are made available in their stead, but other psychic processes are utilized. The

child is taught about reality and shown why it benefits to trade immediate and cruder satisfactions with painful repercussions for slower but more lasting ones which benefit others as well as himself. He is shown that real regard can be gained by working for it, but not by taking things that symbolize regard or by trying to force it from those from whom it should come or by punishing them for its lack.

Education extending so deep as to affect the personality is accomplished more by other means than by purely intellectual ones. Chief of these is identification, whereby the child, through intimate contact with a strong and helpful adult develops admiration and affection for the adult to the point where he wants to be like him and absorb from the adult characteristics which will form a part of his own ideals. The models for the youthful offender need to be admirable people. In addition, the child's character may be influenced by therapy. Here the subtlest and most powerful means of influencing others, positive transference, is engaged. This is a recrudescence of the trustful component of the child's early feelings for his parents.

The best teacher should not scorn work in this field where efforts may accomplish more than with normal children. Here he performs a double service, not only the development of the individual but also the prevention of misery the continuing delinquent child may bring to himself and others. This is true likewise for the psychiatrist working with delinquents. When he rehabilitates a neurotic, he saves the neurotic from misery and gives him and the community the benefit of a well man's constructive services. When a delinquent is saved, not only are these same things obtained, but the community is spared his destructive actions and example.

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## MENTAL DEFICIENCY

E. ARTHUR WHITNEY, M.D.

### Introduction

The trend of scientific thought on the problems of Mental Deficiency now shows a definite leaning toward post-war problems when the civil way of life will replace the military way of life. What will be the attitude of physicians, teachers, psychologists, sociologists, and statesmen when confronted with the problem of the mental defective in the new type of civilian life in the postwar period? What new leaders of thought will succeed Churchill, Roosevelt, Stalin, and Chiang Kai-shek? How will they regard these unfortunate members of society? Where in the "four freedoms" will the mental defective find his niche?

There were in our democracy certain definite trends of thought regarding the problems of mental deficiency in the 1920's and 1930's. Some of these seem destined to be a part of the future program for mental defectives and some, no doubt, will be discarded. Among these, professional men in this field expect the following to be continued and advanced:

1. Early recognition and state-wide registration of subnormal children of school age.
2. A state-wide program for social control of mental defectives.
3. More rigid and nation-wide laws governing marriage of mental defectives.
4. A broader use of selective sterilization as a part of state and national programs of preventive medicine.

5. Increased interest in research in mental deficiency along medical, psychological, and sociological lines.

6. Revision of the systems of special education to eliminate as far as possible stigmatization.

7. Development of positive community programs for subnormal children with community supervision and control.

8. Increased use of parole from institution to communities with adequate local programs for parolees.

Leaders in this field are inclined to believe that the following policies will be noted in the new era:

1. Elimination of civil service program for attendants, cooks, orderlies, nurses, matrons, social workers, and teachers in state and county owned and operated institutions.

2. Less stress will be placed on psychometric analyses alone in the diagnosis and prognosis of suspected cases of mental retardation. Newer instruments with fewer factors of error will be developed and used.

3. Public school education will be more practical and less academic, with manual and physical education playing a larger rôle. The basic theme will be "learning by doing."

4. In the institutional program there will be a swing of the pendulum away from central bureaucratic control, and more responsibility will be placed in the trustees and superintendents.

### Mental Defectives and the War Effort

Menninger<sup>1</sup> presented the problem of the mental defective and the Army in the light of his experience. First, he outlined the Army method of screening at the four levels of study: (1) The induction center rejects those who are poten-

tially unfit as soldiers; (2) the reception center puts the candidate through several tests to evaluate him and place him where he can function most effectively; (3) at the replacement training center those who are maladjusted are further studied and given special training, if indicated, or are eliminated from Army service; (4) the station and general hospitals have the final disposition in some cases, after study to evaluate the man's mental status and his future disposition.

"The Army cannot use a mentally retarded individual who is incapable of following simple instructions and our official directive indicated that *men with a mental age of eight or less are not desirable in the Army.*" Menninger goes on to say that many with mental ages above eight are undesirable because of unstable personalities.

Fifty-two selectees rejected for psychiatric reasons were analyzed by Solomon.<sup>2</sup> The group, in his opinion, represented a cross section of the types which are eliminated from military service for psychiatric reasons. The group included these classifications:

1. Psychoneurotic personalities.
2. Pre- and postpsychotic personalities.
3. Epileptics.
4. Subnormal (mentally retarded).
5. Cases of speech defects.
6. Psychopathic personalities with alcoholism.
7. Patients with postconcussion syndrome.
8. Chronic anxiety hysteria.
9. Acute psychoneurosis.

The basic need for the fighting forces is for men who are "fit to fight"—young, vigorous, healthy men physically fit and with a mind to fight and the "will to win." Rowntree<sup>3</sup> states that the induction requirements now are determined by:

1. The size and composition of the available pool of men;
2. The size of the projected military establishment;
3. The urgency of the need, and

4. (To a lesser extent) the need for effective manpower on the production line.

With Pearl Harbor came:

1. Need for immediate expansion.
  2. Immediate lowering of induction requirements.
  3. Use of 1-B men by the Army.
  4. Change in character of examination both in Selective Service and in the Army.
  5. Correction of certain physical defects within the military establishment.
  6. Extension of age range from 20-28 to 18-45.
- The number of eligible men registered is 29,000,000.  
The number between 18-38 is 22,000,000.  
The number in 4F exceeds 2,800,000.

Rowntree states: "*The most difficult problem of selection is in the field of neuropsychiatry.*" Age is a potent factor in the rate of rejection for psychiatric conditions. At the age of 18, 15 out of 20 qualify, whereas at 45 only 4 out of 20 qualify. Educational deficiency on the other hand decreases with age. At the age of 20, it is 3.8 per 1000, while at 40 educational deficiency shows a rate of 1.5 per 1000. Incidence of mental defects by age from provisional figures shows 2.4.

Brosin<sup>4</sup> reviews the Army's various attempts to rehabilitate "the unfit" instead of abandoning them to their fate. The latest method, too new for adequate analysis of its efficiency, is the "Enlisted Men's Replacement Pool." This unit has a twofold purpose: (1) To build up morale and an acceptance of military life, and (2) provide a medium whereby reasonably intelligent replacements can be made.

Heretofore, the "replacements" have been used in: Military Police, Medical Corps, Quartermaster Corps, and Engineers. In the Military Police, their condition results in inefficient performance. In the Quartermaster and Medical Corps, these men cannot be taken overseas and only a limited number can be used in this country. Brosin states that



they are insufficiently motivated to work willingly and they plead immunity from discipline because of their disability.

Logically, these men should be assigned to engineering battalions, but two massive prejudices deter effective utilization: (1) Congress will not permit Army units to do work which will be in competition with civilians, and (2) "labor battalions" are not tolerated as it seems to reflect in a derogatory manner upon the individual.

In the "News Notes" section of the July issue of the *American Journal of Mental Deficiency*, Butler<sup>5</sup> tabulates the facts regarding boys from the Sonoma (Calif.) State School now in the armed forces:

The rejection rate for 18- and 19-year-old registrants is only slightly lower than rejection rates for older registrants. The most striking difference between the white and negro rejections was "*Educational Deficiency*." This item accounted for only 11.5 per 1000 whites examined, whereas it was the *leading cause of rejection among negroes, accounting for 121.7 per 1000*.

The authors evidently separate "Educational Deficiency" from "Mental Deficiency." The latter caused 6.8 rejections per 1000 whites and 10.0 per 1000 negroes. Mental deficiency had the lowest rate per 1000 among the rejected whites and next to the lowest in negroes.

	Army	Navy	Marines	State Guard	Total	Per Cent
Number known to have been in service....	74	12	4	12	102	100
Number in service at present.....	35	8	1	2	46	45.1
Number in one year with good record.....	8	..	..	..	8	7.8
Number in less than one year with good record.....	28	4	1	5	38	37.2
Number with unsatisfactory record.....	23	4	3	6	36	35.3
Number discharged as mentally unfit.....	10	4	1	5	20	19.6
Number referred for psychiatric study.....	24	4	1	1	30	29.4

Butler believes that *the intellectually inadequate* cannot meet the demands of modern warfare. Their limitations are *at times mistaken for indifference and even disobedience*. He does not feel that the mentally deficient or the socially inadequate should be referred for military service. Their desire to fight, their patriotism, and their sincerity are not questioned, but, handicapped as they are, they become a liability in modern war service.

Rowntree, *et al.*,<sup>6</sup> present a tabulated analysis of rejections among 45,585 reports of physical examination and induction. These reports represent 42,273 white and 3312 negro registrants.

### Amaurotic Idiocy

Amaurotic family idiocy is discussed by Wyburn-Mason,<sup>7</sup> who gives evidence to support his theory that two distinct types of the condition exist: *Type I*—The infantile type almost exclusively found in Hebrew families, which is a self-limited condition fatal within three years; *Type II*—The juvenile type with usual onset at the age of six to eight years, but at times as early as two and as late as 20 years of age. This type is seen most frequently in non-Jews.

Wyburn-Mason discussed the optical signs in the two conditions. He states that in type I at times only optic atrophy occurs, instead of the usual macular

cherry red spot. Eye changes in type II demonstrate a slower course and may also occasionally show optic atrophy instead of pigmentary macular changes, the final retinal picture resembling retinitis pigmentosa. Type II is not related to type I genetically or histochemically.

Marburg's<sup>8</sup> investigation of several cases of infantile amaurotic family idiocy reveals the existence of occlusion bodies and severe secondary nerve cell degeneration. The inclusion bodies are partly argentophilic and partly argentophobic, depending on the type of fat which forms their basis. The significance of inclusion bodies is doubtful; they are observed in parkinsonian states and the senium. Inclusion bodies in amaurotic family idiocy are usually associated with convulsive states or myoclonia. The clinical signs of amaurotic family idiocy are due only in part to the cell changes which affect only the vegetative part of the ganglionic cells. Neurological symptoms appear only when the motor and vegetative parts of the cell are affected. The site of the damage varies in different regions in different cases. All changes seen in the juvenile form are seen in the infantile type if the duration is long enough.

A clinicopathological study, accompanied by photographs of brain sections, of a case of juvenile amaurotic idiocy in a 16-year-old male is presented by Lubin.<sup>9</sup> This case offered an opportunity to correlate the neurologic, psychologic, and electroencephalographic studies made shortly before the patient's death. The similarity among cases mentioned by Sjogren was present, namely: (1) Initial onset of visual disturbances between the fifth and eighth years, progressing to total blindness in one or two years; (2) mental deterioration and behavior disturbances; (3) convulsions; (4) neurological manifestations as tremor, ataxia, etc., and (5) death oc-

curring from 10 to 15 years after the onset.

Histological studies showed characteristic widespread alterations in cell structure throughout the brain. These consisted mainly of: (1) Diffuse lipoidosis and swelling of ganglion cells; (2) completely asystematic, patchlike disappearance of cells, and (3) sclerosis of the molecular layer with loss of tangential fibers. Cortical cell changes decreased in severity from the frontal to the occipital region. In spite of widespread cellular alterations, many cortical functions were retained. The electroencephalographic pattern was not especially impaired.

Lubin, Marburg, and Tamaki<sup>10</sup> present an unusual case. This report concerns a disease occurring in three siblings which does not easily resemble any one disease entity. Clinically, the disease resembles infantile progressive spinal atrophy (Werdnig-Hoffman disease) and histopathologically it is related to amaurotic family idiocy (Tay-Sachs disease).

The disease appeared in the fourth, seventh, and eleventh of 11 children. Clinically, the condition produced a flaccid paralysis with retention of tendon reflexes in two cases, absence of abdominal reflexes, difficulty in deglutition, strabismus, and varying degree of mental impairment.

The disease resembled Tay-Sachs and Werdnig-Hoffman disease in its onset, fatal termination, familial occurrence, flaccid paralysis, and involvement of cranial nerves. It differed from Tay-Sachs disease in the absence of severe mental deterioration and lack of visual disturbances.

Pathologically, the disease resembled Tay-Sachs disease. Alterations were seen in the cells and their processes throughout the entire central nervous system, especially on the spinal cord, brain stem, and cerebellum. Cellular changes con-

sisted of swelling of the cytoplasm, distortion of normal cellular structure, disappearance of the Nissl substance, changes in neurofibrillary structure and disappearance of cells and dendrites. The pyramidal tracts and portions of the posterior column were partially demyelinated. Some of the swollen cells contained hematoxylinophilic granules, indicating the presence of so-called pulipoids.

### Family Care and Parole

Helen Pigeon<sup>11</sup> has prepared a valuable manual for those who will supervise the future of the mental defectives in community life. The importance of the problems of subnormal children is discussed in a comprehensive chapter on "The Behavior of the Individual." She illustrates the fact that mental deficiency has positive social implications, since intelligence is a factor in health, emotional adjustments, and worldly success, and also lack of it can account for various types of antisocial behavior patterns.

Pigeon considers feeble-mindedness a State responsibility and recommends a program to include:

1. Recognition, classification and registration of the mental defectives to demonstrate accurately the size and nature of the problem.
2. Training in the formative years in special classes.
3. Community supervision by public and private agencies.
4. Institutional placement for the maladjustable and special types with special provision for defective delinquents.

The State of New York probably leads all others in family care for mentally retarded and Pollock<sup>12</sup> presents the subject for the future with the projects of prewar Europe as a background.

In prewar Europe there were many instances of successful "Family Care": Belgium's famous "Gheel Colony," Switzerland's "Burgholzli," Scotland's "Kerkealdy," and several others in Germany, France, and England.

Pollock's proposals for the future of family care are:

1. Family care should be continued and expanded.
2. The State should appoint a "director of Family Care."
3. The State should make separate appropriations for "Family Care."
4. The State should establish Family Care Colonies in various sections of the State.

The chief requisites of a family care colony are:

1. A small central receiving hospital for observation and disposition of suitable cases.
2. Groups of families located near the central hospital should receive training for their task.
3. A well-organized plan of operation.

Problem children are considered in four more or less distinct groups by Siewers:<sup>13</sup> The congenitally defective, including both mentally and physically handicapped; the psychosomatic and psychoneurotic; those handicapped as a result of intercurrent disease, and simple behavior problem children. Siewers believes the last group due to either evasion of reality, anxiety, or insecurity. Treatment in all types should be by full analysis of the whole situation.

### Child Guidance

Wallin<sup>14</sup> ably discusses the need, objectives, and methods of guidance for subnormal children. He urges every classroom teacher, as well as school systems and communities, to pay attention to two basic essentials for adequate educational and recreational experiences and the second is provision for an efficient placement service for "graduates" of special classes.

Dr. Wallin reminds us that when this war is over the proper placement of the handicapped child will again present a serious problem. To combat this, he recommends State and national committees to co-ordinate efforts for the placement of these handicapped individuals

now and for their absorption into industry in the difficult post-war period.

Sullivan<sup>15</sup> presents an analysis of the assets and liabilities of high grade defectives in planning for their occupational future. Their weaknesses stand out and it is the responsibility of the institutions and special classes to create opportunities and methods to correct them. Among their limitations are: Weak work habits, poor ability, unwillingness to follow exact directions, lack of the concept of loyalty, lack of appreciation for the proper care of materials and equipment and job truthfulness.

Sullivan recommends that mental defectives be placed in some occupation-training program at the earliest possible age. The occupational curriculum should include many and divergent industrial and occupational activities. It is highly essential to develop systematic and thorough habits of work in order to make the defective acceptable to a future employer. Opportunities for their placement in industry today are many, but such opportunities will continue to be available only if their work records in industry prove satisfactory.

Gesell and Ilg<sup>16</sup> have presented a book that may well be a guide in future social planning and practices regarding the philosophy of child development and guidance. It is presented in three major divisions:

1. Child growth in relation to modern culture.
2. The growing child envisaged from the standpoint of his own development of progress.
3. Guidance and growth in terms of developmental philosophy.

Abel and Kinder's book on the *Adolescent Subnormal Girl* deals exclusively with girls of dull, normal, borderline, or moron levels of intelligence between the ages of 14 and 19. The authors contend that: "The greatest obstacles to the scientific study and care of the subnormal

girl are widespread prejudices and the prevalence of erroneous ideas as to the causation and treatment of the condition of subnormality." This volume should aid in correcting these obstacles.

The rôle of a subnormal girl as a potential mother presents a complex problem for society. Society desires effective control but offers little in the way of a satisfactory solution. The challenge is to all social-minded persons concerned with problems of human adjustment. All professionally interested workers will find this volume one of stimulating interest.

Rautman<sup>17</sup> presents present-day principles for adequate institutional educational programs for subnormal children in stressing a program based "upon each pupil's past history, his present abilities, and his probable future needs." He states that: "The curriculum for the mentally defective must have a staircase structure, in that it is made up of numerous specific and definite goals, each a useful end in itself."

Several institutions for the subnormal have made attempts to teach their inmates the rudiments of government. Janvier<sup>18</sup> reports the results with a group of adolescent institutionalized girls. Four salient points are presented:

1. Some effects of individual personalities on each other.
2. The types of problems which interest or bother the group.
3. The girls' attitude towards themselves, their group, and society, which seems to result from institutional life.
4. The gradual development of a basic understanding of democratic processes.

### Mental Deficiency and Crime

Penrose<sup>19</sup> presents some interesting statistics on the relationship between mental deficiency and crime and his figures show a definite relationship to similar data from European and South African sources. One quite significant statement is: "The prevalence of serious

crimes, especially those which imply violence against the person, appears to be much more marked in countries which provide relatively few beds for mental patients. The suggestion is that countries and States which have positive mental health programs show good records in crime prevention. States like New York and Massachusetts have relatively less crime per capita than most others and these States have a high rate of admission into institutions for mental defectives."

### Racial Distribution

Malzberg<sup>20</sup> has presented some enlightening statistics regarding racial factors in children admitted to New York State Schools for Mental Defectives. In his study it appears that negroes showed a striking relative excess of first admissions over the white population. With the white children, females showed a lower rate of first admissions than males.

Whites are studied on the basis of ancestral stock: Italian, Irish, German, English, Scandinavian, Polish, and Russian. Analyzed in this way, he shows that Italians have a high rate of mental deficiency, whereas in the Polish and Scandinavian it is relatively low. According to his table of "standardized" average annual rate per 100,000 population, the figures are:

Negroes, 16.1; Italians, 9.4; English, 8.0; German, 7.1; Irish, 6.8; Russian, 6.8; Scandinavian, 6.2, and Polish, 4.8.

### Brain Injury, Etc.

Werner and Strauss<sup>21</sup> at Northville, Michigan, report an interesting study of two groups of 20 retarded children, one with evidence of early acquired brain lesion and one without. A series of tests was utilized, consisting of object pictures, animal pictures, etc. They noted that the child with brain injury showed

marked tendencies toward formation of unusual relationships in describing the pictures which the authors interpret as due to "certain peculiarities of the thought processes." One factor noted was a trend on the part of the brain-injured child to pass far beyond the given situation in space and time, whereas the control group restricted themselves rather realistically to the immediate situation.

Three general groups of malformations are discussed by Michelsen:<sup>22</sup> (1) Developmental defects of the skull; (2) developmental defects of the intracranial structures: (a) Brain and meninges; (b) cerebrospinal fluid system, (c) vascular system; (3) congenital tumors.

He discusses cerebrospinal fluid system malformations first, since an analysis of this condition helps in the basic understanding of other conditions. Congenital malformations include occlusion of the aqueduct of Sylvius; absence of the foramina of Lushka and Magendie; and absence of cisterns. In adults, nonneoplastic aqueduct stenosis is rare. Surgical treatment and cure of congenital obstructions are discouraging. In adults, aqueduct obstruction is handled by short-circuiting the fluid past the obstruction by buried rubber catheters. In congenital hydrocephalus, the method of endoscopic coagulation of the choroid plexuses in the lateral ventricle is useful in selected cases.

There is a variety of types of complete and incomplete craniostenoses for which several operative procedures to facilitate the normal expansion of the growing brain have been suggested. These include: *Linear craniectomy*, *circular craniectomy*, *subtemporal decompression*, and the so-called "*mosaic operation*."

A developmental anomaly of the occipital bone, known as basilar invagination of the skull, is not uncommon. In this

condition, a *suboccipital decompression and laminectomy* of the upper two cervical vertebrae affect good results.

The surgical treatment of the Arnold-Chiari syndrome of a basilar herniation associated with spinal meningocele is gratifying. It consists of a *simple decompression of the posterior fossa and the upper cervical cord*. The arachnoid is opened widely when it can be done easily, but adhesions are not disturbed because of risk involved.

Meningoceles of uncomplicated type should always be repaired surgically. Porencephaly and micrognathia in selected cases may be handled by the historic *trephination of the skull*.

Circulatory abnormalities, such as aneurysms, are not particularly amenable to surgery except the large aneurysms of the carotid artery, angioma arteriale, and cerebellar hemangiomas.

Congenital epidermoids respond to surgical treatment if accessible. Cranio-pharyngiomas are epithelial tumors from the remains of Rathke's pouch. The surgical treatment of this condition in the past has been unsuccessful, now by means of *transcortical transventricular exploration* with drainage into the ventricular system better results are obtained.

### Laurence-Moon-Biedel Syndrome

Lurie and Levy<sup>23</sup> report two cases of the Laurence-Moon-Biedel syndrome with somewhat unusual combinations of hereditary deviations. About 150 cases of this syndrome have been reported since first described by Laurence and Moon in 1866. Lurie and Levy's cases presented a combination of obesity, genital dystrophy, dwarfism, deafness, mental deficiency, syndactylism, and familiar occurrence. They represented

rather incomplete pictures of the syndrome.

Many theories have been advanced to explain the syndrome, but Biedel's idea of a familial form of dystrophy, adiposogenitalis of cerebral rather than pituitary origin, seems to be the most tenable. In these patients the typical Frölich's syndrome with increased sugar tolerance and delayed development of bone tissues confirms the assumption of a genetic factor in the condition.

In their cases, Lurie and Levy report for the first time electroencephalographic studies. No definite classification or localization was possible and no epileptic waves were recorded. The androgen test, also reported for the first time, shows low values indicating gonadal dysfunction.

Snell<sup>24</sup> reports a case of Laurence-Moon-Biedel syndrome in a female negro with all the cardinal features of the syndrome except hypogenitalism. This 13-year-old girl, one of a family of seven, had definite retinitis pigmentosa plus nystagmus and macular degeneration. Mental deficiency, polydactylism, and obesity were also present. Related ocular and skeletal defects were seen in a sister aged 21.

Laurence-Moon-Biedel syndrome found in three patients in India is reported by Kutumbiah and Abbu.<sup>25</sup> Retinal degeneration, obesity, hypogenitalism, polydactyly, and mental deficiency were present in each case. One case showed a family history of polydactyly, and consanguinity of parents was present in the other two cases.

The fundus in all three showed definite retinitis pigmentosa. The Frölich type of obesity and hypogenitalism was evident in each case.

Treatment in these cases is discouraging. *Endocrine therapy*, particularly *pituitary therapy*, is usually tried with

very little result. *Thyroid extract* and *theelin* have shown no appreciable response.

### Phenylpyruvic Oligophrenia

Dann,<sup>26</sup> *et al.*, report the case of an infant of two years showing marked phenylpyruvic oligophrenia. The disease is characterized clinically by marked mental deficiency with athetosis or other neurological conditions. This child always excreted from 0.45 to 1.03 Gm. of phenylpyruvic acid in the urine per 24 hours. The administration of *d,l-phenylalanine* (1.5 Gm.—22½ gr.—per kg.) caused prompt rise in the output of the acid. The use of *l-tyrosine* in similar dosage showed no effect. Large doses of *ascorbic acid* likewise showed no effect.

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## OPHTHALMOLOGY

*Edited by* CONRAD BERENS, M.D., and JOSHUA ZUCKERMAN, M.D.

### Aniseikonia

**Significance**—H. M. Burian<sup>1</sup> discusses the clinical significance of aniseikonia. He points out that, normally, discrepancies exist between the neuromuscular apparatus, the dioptric system, and the sensorial apparatus of one eye and that of the other. Some of these incongruities are necessary for normal binocular vision and depth perception. However, when these exceed a certain amount they interfere with fusion and produce symptoms. One of these incongruities is aniseikonia. Aniseikonia may occur in

cases in which differences in the dioptric images are present as in anisometropia (refractive aniseikonia) as well as in cases in which these differences are absent (basic aniseikonia). Variations in the size and shape of the images may occur.

### Chemotherapy

**Toxic Reaction** (*Membranous Conjunctivitis*)—An unusual type of toxic reaction following the administration of 18 Gm. (5 drachms) of *sulfathiazole* is reported by I. M. Schnee.<sup>2</sup> The eyelids became inflamed and swollen, the



mouth became sore, the lips cracked, and a gray membrane developed on the conjunctiva and the mucous membrane of the mouth and throat. Removal of the membrane left no bleeding surface and the membrane re-formed within a few hours. After discontinuance of the chemotherapy rapid recovery occurred.

### Choroid

**Hemorrhage—Treatment**—Immediate *venesection* for the control of choroidal hemorrhage following intracapsular cataract extraction is recommended by J. J. Regan.<sup>3</sup> The procedure seems to be a safe and simple method for checking choroidal hemorrhage and may also be useful in cases of separation of the choroid and in hyphemia with blood staining of the cornea.

**Malignant Melanoma**—A discussion of multiple primary malignant neoplasm is presented by M. K. Asbury and D. Vail.<sup>4</sup> An intraocular malignant melanoma of the choroid, and a glioblastoma multiforme of the cerebrum are reported. The former developed from a nevus that had been observed for three years before it increased in size.

### Color Blindness

**Treatment**—The treatment of color blindness in individuals who had been rejected by the armed forces for mild red-green blindness is discussed by H. Cadan.<sup>5</sup> He administered vitamin A and vitamin B-complex subcutaneously and orally, tincture of iodine orally, faradism and sinusoidal current locally, and taught the patients to study colors on the Edridge-Green lantern, yarns, and Stilling and Ishihara charts. After from 6 to 15 treatments, 35 passed re-examination in various branches of the military service and normal color perception still persisted six months after treatment.

## Conjunctiva

**Burns and War Gases—Treatment**—C. Berens and E. Hartmann<sup>6</sup> discuss the effect of war gases and other chemicals on the eyes of the civilian population. The gases may be vesicant, lung-irritating, sternutatory, and lacrimatory. Immediate irrigation of the conjunctival sac with *water* or *sterile salt solution* (preferably 1.4 per cent) and instillation of light *liquid petrolatum* is recommended for the immediate treatment of all burns except those caused by mustard gas, for which neither oils nor ointments should be used for several days. It is important that the applied solution should be sterile to lessen the danger of secondary infection.

For acid burns of the eye, J. M. Carlisle and A. Gibson<sup>9</sup> recommend instillation of a buffer solution of *sodium bicarbonate* (2 per cent) into the conjunctival sac until a neutral reaction of the secretion of the fornices is obtained; for alkali burns, instillation of a buffer solution consisting of *acetic acid*, 2.5 Gm. (37.5 gr.) *sodium acetate*; 3 Gm. (45 gr.) *sodium chloride*; 4.5 Gm. (67.5 gr.), and distilled water, 1000 cc. (34 fluid ounces), every 3 minutes for 30 minutes or until the reaction of the secretion in the fornices is neutralized; and for lime burns, a solution of *ammonium tartarate* (4 per cent).

**Catarrhal Conjunctivitis—Treatment**—According to P. Thygeson and A. E. Braley,<sup>7</sup> treatment of catarrhal conjunctivitis with *sulfonamide* in an ointment base consisting of 25 per cent hydrous wool fat and 75 per cent petrolatum produced better results than treatment with *silver nitrate* or *mercury oxycyanide*. In nonstaphylococcic catarrhal conjunctivitis, sulfonamides offer no advantages over ordinary therapy; but in acute conjunctivitis of bacterial origin, treatment with sulfathiazole is

valuable. Most cases of severe blepharitis or of meibomianitis and of non-bacterial infections, including trachoma, are resistant to sulfonamide compounds. Allergy to the sulfonamides occurred in some cases.

**Nevi—*Diagnosis***—The use of the filtered ultraviolet light from the mercury-vapor lamp for diagnosing unpigmented nevi and melanomas and for delimiting their size is discussed by T. L. Terry.<sup>8</sup> Under filtered ultraviolet light, these lesions present their true melanin color and appear larger than when viewed by ordinary illumination. Ultraviolet light should, therefore, be used as a guide to their complete removal. In many cases, when the extent of the lesions is realized, surgeons will be less eager to attempt surgical removal.

### Contact Lenses

**Impression Material**—The use of zelex, a flexible colloidal material employed in dentistry, is recommended by P. H. Boshoff<sup>10</sup> for taking impressions of the eye for molded contact glasses. When dissolved in water, the zelex powder sets into a firm elastic mold.

### Cornea

**Fatty Dystrophy**—J. A. Conway and A. Loewenstein<sup>11</sup> report a case of primary symmetrical interstitial fatty corneal dystrophy with lipoidal arc formation. The condition was characterized by a broad lipoidal arc with an irregular lucid interval between the arc and the sclera and infiltration of the entire cornea with small grayish-white fatty droplets.

**Foreign Body Removal**—For removal of a foreign body of the cornea, G. F. Harding<sup>12</sup> recommends the use of a hypodermic needle into which a hollow, chrome-plated brass handle is fitted. The needle can be sterilized by

boiling instead of by immersing in antiseptic solution as is the usual procedure when corneal spuds are used.

**Interstitial Keratitis**—A case of bilateral interstitial keratitis associated with bilateral gummatous infiltrations of the uveal tract is reported by J. D. Freeman.<sup>13</sup> Loss of both eyes occurred within a period of six months.

**Neuroparalytic Keratitis—*Treatment***—M. Klein<sup>15</sup> recommends the use of contact lenses for the treatment of neuroparalytic keratitis. He reports two cases in which clearing of the cornea and improvement in visual acuity were obtained. In one case, the keratitis followed operation for an acoustic tumor; in the second case, the keratitis followed an injection of alcohol for trigeminal neuralgia.

**Virus Keratitis—*Treatment***—According to J. B. Hamilton,<sup>16</sup> a bacterial keratitis can be readily differentiated clinically from a virus keratitis. Virus keratitis usually follows a period of pyrexia; acute iritis and conjunctival discharge are absent; corneal lesions or disciform keratitis may be present; and cultures are negative or contain saprophytes. Moreover, recovery is usually rapid and the visual results are good.

In treating virus keratitis, heat or artificial pyrexia should be avoided. **Iced compresses** are useful. **Tincture of iodine** is useful for herpes of the lips; **carbolic acid** for dendritic ulcers; and **silver nitrate** for marginal and superficial punctate keratitis.

**Allergic Keratoconjunctivitis**—Five cases of allergic keratoconjunctivitis which resulted from oranges, butyn sulfate, hydrous wool fat, a proprietary inhalant, and a fur coat, respectively, are reported by C. S. O'Brien and J. H. Allen.<sup>14</sup> The tissues of the eye may also become hypersensitive to atropine, pontocaine, sulfathiazole, cosmetics, and

foods. In these cases the history usually reveals recurrent attacks of redness and swelling, itching, and desquamation of the eyelids, congestion of the bulbar conjunctiva, lacrimation, and mucopurulent discharge. If keratitis develops, it is characterized by yellow infiltrates situated just within the limbus so that a narrow zone of normal cornea separates the limbus from the lesions. The infiltrates do not stain. Patch tests or the introduction of suspected material into the conjunctival sac are useful, but injection and scratch skin tests are not satisfactory. Either desensitization by intradermal injection or removal of the allergen is necessary to obtain relief.

#### **Dendritic or Herpetic Ulcer—**

**Treatment**—A report of 12 cases of herpetic or dendritic ulceration of the cornea, in which permanent healing without recurrence occurred only after foci of infection were eliminated, is made by F. O. Schwartz.<sup>17</sup> In all cases foci of infection were found in the sinuses, tonsils, or teeth. He believes that a relationship exists between these foci (an unidentified virus) and the corneal ulcers because improvement occurred only after these foci were removed.

**Vascularization**—Observations on the effect of riboflavin on vascularization of the cornea and on the symptoms of fatigue in Royal Canadian Air Force personnel are described by F. F. Tisdall, J. F. McCreary, and H. Pearce.<sup>18</sup> Vascularization is common in association with other symptoms attributed to lack of riboflavin—fatigue, aching, and watering of the eyes, a sandy sensation, headaches, dizziness, reading intolerance, and decrease in visual acuity.

In a series of cases routinely exposed to glare, the administration of 9.9 mg. of *riboflavin* daily for a period of two months decreased the vascularity in 70 per cent of cases and improved the symp-

toms in 95 per cent of cases. When riboflavin was administered to another group for only half this period of time, decrease in vascularity was less marked, but the relief from symptoms was just as noticeable. Vascularization of the cornea was recorded by means of a photographic device. It is concluded that vascularization of the cornea is common and dependent upon riboflavin-containing foods in the diet; large dosages of riboflavin decrease the vascularization in a large number of cases and relieve the symptoms of fatigue of the eyes of fliers who are exposed to glare.

### **Drugs**

**Eye Solutions**—According to N. C. Elvin,<sup>19</sup> an ideal ophthalmic solution should have a pH of 7.4 and should be isotonic with a 1.4 per cent solution of sodium chloride to resemble normal tears in hydrogen ion concentration and in osmotic pressure. Such a solution is most effective because it is least irritating and most easily absorbed.

### **Eye**

**Disease**—A discussion of viruses of ocular importance is presented by P. Thygeson.<sup>20</sup> He points out that the viruses of inclusion blennorrhoea, herpes simplex, and herpes zoster frequently affect the eye; those of variola, vaccinia, and lymphogranuloma venereum rarely affect the eye. The viruses of psittacosis, dengue fever, foot and mouth disease, rabies, lymphocytic choriomeningitis, and canine distemper affect the eye still more rarely. The etiology of the following diseases is considered to be a virus; acute follicular conjunctivitis of Béal, chronic follicular conjunctivitis, ocular pemphigus, dermatitis herpetiformis, superficial punctate keratitis, epidemic, and other types of keratoconjunctivitis, chronic catarrhal conjunctivitis, and erythema multiforme.

**Intraocular Foreign Body**—A case of multiple intraocular foreign bodies sustained while stamping out steel airplane parts on a hand press is described by R. A. D. Crawford.<sup>21</sup> After several attempts, the foreign bodies were removed by the anterior route through a keratome incision with the aid of a magnet. (EDITOR'S COMMENT: This case is reported to point out that in injuries of this kind it is not sufficient to be content with locating the foreign body; it is important to remember that foreign bodies may be multiple.)

**Infections—Treatment**—J. G. Bellows<sup>22</sup> discusses chemotherapy in ophthalmology. Oral administration of *sulfonamides* is effective in ocular complications of erysipelas, gonorrheal ophthalmia, trachoma, inclusion blennorrhea, lymphogranuloma venereum, panophthalmitis, and sympathetic ophthalmia. Local application is useful in pyogenic dermatosis, infectious blepharitis, and acute conjunctivitis.

After oral administration, only *sulfanilamide* and *sulfapyridine* reach the fluids and tissues of the eye in adequate concentration to be effective in the treatment of intraocular infection. However, *sulfathiazole* and *sulfadiazine* are not contraindicated because these drugs may be concentrated in the eyes by heat, mecholyl, paracentesis, or inflammation resulting from infection.

After local application, only sulfanilamide penetrates the eye in adequate concentration. Other sulfonamides may be rendered more effective by iontophoresis. Application to the denuded cornea retards healing and increases scar formation.

### **Eyeball**

**Exophthalmos—Differential Diagnosis**—The value of roentgenography in cases of exophthalmos is pointed out by R. L. Pfeiffer.<sup>23</sup> It is useful not only for

the elimination of extraorbital diseases or conditions as possible causes of exophthalmos but also for the detection and for differential diagnosis of some of the tumors of the orbit. Roentgenographic findings were positive in about 70 per cent of 200 consecutive cases of exophthalmos; indicative or diagnostic in 42 per cent; and suggestive in an additional 20 per cent of cases. X-ray was not informative in nearly one-fifth of the cases. The findings were most informative in retention cyst, meningioma, craniostenosis, neurofibromatosis, deformity of the orbit, glioma of the optic nerve, pseudotumor, hyperthyroidism, and oculomotor paralysis.

**Pulsating Exophthalmos**—A discussion of pulsating exophthalmos and a report of a case which was cured spontaneously in a woman, 87 years of age, is reported by A. D. Woods.<sup>24</sup> The exophthalmos had resulted from a fall.

Pulsating exophthalmos may result from rupture of the carotid artery into the cavernous sinus, aneurysm of the internal carotid artery into the cavernous sinus, aneurysm of the ophthalmic artery within or outside the orbit and from tumors in or outside the orbit. The most common type is the carotid-cavernous aneurysm which usually results from trauma.

According to Woods, a complete or partial, immediate or gradual carotid ligation is indicated.

**Treatment**—Five cases of pulsating exophthalmos which were treated by ligation of the carotid artery are reported by J. D. Martin, Jr., and R. F. Mabon.<sup>25</sup> Early *ligation of the carotid artery* should be performed before extensive proptosis develops. Surgical treatment is beneficial, but in many cases little or no improvement results. They state that no direct operation for obliterating the fistula is satisfactory.

**Glaucoma—Associated with Nevus Flammeus**—A case of nevus flammeus associated with glaucoma, in which cyclodiathermy was used to control the intraocular pressure, is described by B. Y. Alvis and V. A. Toland.<sup>26</sup> A boy, 14 years of age, presented a nevus flammeus, the outline of which conformed to the skin distribution of the ophthalmic and maxillary branches of the right trigeminal nerve on the skin of the face and on the mucous membrane of the nose and throat. In one eye, the tension was 16 mm. Hg. (Schiötz) and in the eye on the affected side it was 43 mm. Hg. (Schiötz). The patient's vision diminished in spite of the use of *pilocarpine solution* and *suprarenin ointment*. A *corneoscleral trephining* was performed which controlled the tension for a period of ten months. When the tension began to rise again and field changes continued progressively, a perforating *cyclodiathermy* was performed at the upper half of the ciliary region. A sheath of telangiectatic blood vessels was found on the sclera and below Tenon's capsule which encircled the eyeball. The tension remained 15 mm. Hg. for one month, then rose to 27 mm. A cyclodiathermy operation was then performed on the lower half of the ciliary region. Five months later the tension was 16.5 mm. Hg. (Schiötz) and vision with correction was 5/7.5. It is concluded that the effectiveness of this method of treatment cannot be determined yet.

**Treatment**—The value of *furmethide* is compared by E. Uhler<sup>27</sup> with that of other miotics for the treatment of glaucoma. Furmethide is a parasympathomimetic drug which reduces intraocular pressure in glaucoma. A 10 per cent solution is as effective in primary acute glaucoma as a 20 per cent solution of *mecholy* combined with a 5 per cent

solution of *prostigmine*. The latter is probably preferable in early cases, furmethide in advanced cases. Moreover, a 10 per cent solution of furmethide is more effective than a 2 per cent solution of *pilocarpine* in chronic glaucoma, but it cannot be relied upon to maintain normal intraocular pressure indefinitely.

## Eyelids

**Dermatologic Lesions**—O. S. Ormsby<sup>28</sup> discusses the following dermatologic lesions about the eyes: Ocular pemphigus, ectodermosis erosiva pluriorificialis, the triple symptom complex of aphthous ulcers in the mouth, retinitis and iridocyclitis, avitaminosis, contact dermatitis (dermatitis venenata), xanthelasma, pseudoxanthoma elasticum and angioid streaks, and lupus erythematosus.

**Diagnosis and Treatment**—In *ocular pemphigus*, a slow, progressive shrinking of the conjunctiva occurs as part of pemphigus of the mucous membranes of other parts of the body. Shrinkage of the conjunctiva may also occur in bullous dermatitis herpetiformis following vaccination; erythroderma ichthyosiformis, epidermolysis bullosa dystrophica acquisita, and in congenital syphilis.

*Ectodermosis erosiva pluriorificialis* is a form of erythema multiforme accompanied by conjunctivitis in association with affections of the mucosa of the nose, urethra, vagina, and anus. The ocular symptoms may be severe enough to cause partial or total blindness.

*Avitaminosis*—deficiency of vitamin A and vitamin G (B<sub>2</sub>) or riboflavin—is associated with night blindness, keratomalacia, and follicular hyperkeratosis. The condition responds to the administration of cod liver oil. The symptom complex due to riboflavin deficiency is characterized by an eruption at the angle of the mouth, scaly inflammation of the vermilion portion of the lips, dermatitis

of the nasolabial folds and of the inner and outer canthi of the eyes, vascularizing keratitis, circumcorneal injection, corneal opacities, and iritis. *Riboflavin*, 5 mg., thrice daily, is effective. Natural sources of riboflavin are milk, eggs, liver, muscle, and yeast. The natural sources of vitamin A are butter, cream, egg yolk, fish-liver oils, and green leafy vegetables.

*Contact dermatitis* usually appears as an erythema of the eyelids followed by vesicles, papules, crusts, or scales. It is most frequently caused by cosmetics, hair dyes, hair lotions, and nail polish. *Sodium thiosulfate*, 1 Gm. (15 gr.), intravenously every other day for a week and 10 per cent *naftalan ointment* locally are advised by Ormsby.

*Xanthelasma*, according to Ormsby, may be excised or treated by application of *carbon dioxide snow*. (COMMENT: The application of deliquesced crystals of *trichloroacetic acid* is efficacious and painless.)

*Pseudoxanthoma elasticum* and *angioid streaks* are commonly associated. Symmetrical discrete chamois-yellow to orange pea-sized papules assume a linear arrangement or merge to form a plaque on the neck or in the axillary and articular folds, the cubital and popliteal spaces, and in the groin but not on the palms and soles. In both eyes angioid streaks appear as jagged, irregular, brown lines beneath the retinal vessels which radiate like the spokes of a wheel from a peripapillary ring of the same appearance or the brown lines branch and anastomose.

*Lupus erythematosus* affects the conjunctiva, eyelids, and eyelid margins. Redness, edema, photophobia, mucoid discharge, and atrophic areas develop. The eyelid margins become rounded and devoid of hairs. The skin lesions are red, scaling, well-defined patches which later become atrophic. *Gold sodium thiosul-*

*fate*, 10 to 50 mg., intravenously at weekly intervals, is specific according to Ormsby. Intramuscular injection of *bismuth*, 0.2 mg., is also effective.

## Eyelids

**Mollusum Contagiosum**—It is pointed out by L. A. Julianelle and W. M. James<sup>29</sup> that mollusum contagiosum of the eye is uncommon. This condition resembles marginal chalazia, milia, and warts and may cause persistent conjunctivitis and even keratitis. Histologic examination of the growth is infallible. Unlike most diseases caused by viruses, the degree of infectivity of mollusum contagiosum is low; the condition remains monocular and does not spread to the family. The virus has been propagated on chorioallantoic egg membrane in two out of four attempts.

**Malignant Neoplasms—Treatment**—*Contact roentgen therapy* in superficial malignant lesions about the eye is recommended by W. E. Howes and M. R. Camiel.<sup>30</sup> The apparatus used for this type of therapy consists of a tube fitted into a compact shockproof metal cylinder. The rays emerge from one end like the light from a flashlight. The target is 1.8 cm. from the face of the tube. The intensity of radiation at the lesion is greater than with the conventional types of apparatus used at a target-skin distance of 30 to 50 cm. Many lesions are cured by doses of from 10,000 to 13,000 r. applied at one sitting. Superficial basal-cell carcinoma can be destroyed in 60 seconds.

**Rosacea—Treatment**—A discussion of ocular rosacea is presented by G. Wise.<sup>31</sup> He is of the opinion that ocular rosacea and facial rosacea are manifestations of the same disease. The cause of rosacea is unknown but the condition is due to a factor which causes vasodilatation in the facial area. Negroes are

not affected. Rosacea is not a manifestation of riboflavin deficiency, of gastrointestinal disturbances, lowered gastric acidity, focal infection, or endocrine disorder. Secondary infection with staphylococci produces most of the symptoms. These symptoms can be arrested by treatment with 5 per cent *sulfathiazole* or *sulfadiazine ointment*.

**Xeroderma Pigmentosum**—Four cases of xeroderma pigmentosum of the eyelids associated with ocular complications resulting in symblepharon and atrophy of the eyelid with exposure and ulceration of the cornea and conjunctiva are reported by A. B. Reese and I. E. Wilber.<sup>32</sup> The lesions resemble freckles, represent an abnormal reaction to light, and are potentially cancerous. Three of the patients were siblings. In one case, an epithelioma of the cornea developed at the site of an ulcer. Two patients died at 7 and 11 years, respectively, two are now 16 and 30 years, respectively.

Four stages of the disease are described—erythema, pigmentation, atrophy, and malignant change. The skin is normal at birth but erythema develops after exposure to sunlight, usually before the second year of life. This erythema differs from ordinary sunburn in that it takes longer to disappear. The condition is at its worst at about the sixth year of life and death usually occurs before the twenty-first year as a result of inanition, hemorrhage, or meningitis, following ulceration of the orbital or nasal cavities.

Treatment is palliative. Protection from sunlight is advocated by remaining indoors during daylight hours, wearing veils and glasses and applying ointments. If keratosis develops, *fulguration* or small amounts of low-voltage *x-ray therapy* are helpful. If neoplasms of cornea or of areas about eyes occur, *excision* or *irradiation* is necessary.

## Fundus

**Diseases — Treatment** — The use of vasodilators in acute diseases of the fundus is discussed by F. C. Cordes.<sup>33</sup> The rationale of this treatment is based on the assumption that the lesions result from vasospasm which interferes with the available oxygen essential to the normal functioning of the capillaries and tissues. Therefore, vasodilators should be beneficial. To produce rapid maximum vasodilatation, *typhoid vaccine* is injected intravenously daily, starting with 7,500,000 killed organisms on the first day, 8,000,000 the next day, 9,000,000 on the third day, and 10,000,000 on the fourth day. In some cases this may be adequate but it is often advisable to supplement the typhoid therapy with subcutaneous injections of 10 mg. of *sodium nitrate* daily for a period of two to six weeks and to continue as long as demonstrable improvement occurs. In other cases sodium nitrate alone may be used, 50 mg. being injected as an initial dose and increased to 100 mg. if no reaction ensues. *Depropanex*, a deproteinized pancreatic extract, may be administered instead—1 cc. (16 minims) intramuscularly twice a week for a total of 16 to 18 doses. Tobacco, exposure to cold, psychic trauma, worry, and excitement should be avoided.

The following lesions seem to respond to vasodilator therapy: Acute retrobulbar neuritis, optic neuritis, acute exudative choroiditis, chorioretinitis juxtapapillaris (Jensen), tubercular choroiditis, acute closure of the central retinal artery and central angiospastic retinopathy.

The results of treatment were most satisfactory in cases seen early in the course of the disease; but they were disappointing in lesions which had existed for a long period of time and in chronic fundus lesions in elderly patients.



## General Diseases

**Mercurialism**—A brownish-colored reflex from the anterior capsule of the lens was observed by W. S. Atkinson<sup>34</sup> in mercurialism. The slit lamp revealed that the reflex was lusterless, somewhat homogeneous, and that the color was deeper in the pupillary area. By oblique illumination, the lens usually presents a dull-gray appearance but it is perfectly clear by ophthalmoscopy. The brownish-colored reflex is permanent and is attributed to a deposit of mercury on or in the anterior capsule of the lens. Vision is unaffected. Other manifestations of chronic mercurialism are intention tremor, gingivitis, caries and loosening of the teeth, and bone destruction or absorption. Atkinson concludes that the colored reflex is probably an early diagnostic sign of chronic mercurialism.

**Multiple Sclerosis**—The ocular manifestations of multiple sclerosis are enumerated by B. J. Larkin.<sup>35</sup> They include retrobulbar neuritis, diplopia, nystagmus, abnormal pupillary reactions, optic atrophy, papillitis, and papilledema.

**Relapsing Fever**—A report of nine cases of relapsing fever in which ocular complications developed is presented by J. B. Hamilton.<sup>36</sup> All cases were associated with intense headaches; four cases with iridocyclitis; one with facial paralysis. Spirochetes were isolated in only two cases. The prognosis of relapsing fever is favorable.

## Iris

**Leiomyoma**—A case of leiomyoma of the iris in a white woman, 46 years of age, is reported by J. E. Kahler, W. E. Wallace, R. Irvine, and A. R. Irvine.<sup>37</sup> The tumor arose from the dilator muscle of the pupil, that is, its origin was epiblastic. Because metastasis did not occur, they conclude that leiomyoma of the iris is benign. Only seven cases of lei-

omyoma have been reported in the literature.

## Lacrimal Drainage System

### Congenital Absence—Treatment—

A case of tearing associated with absence of the upper and lower puncta, the lacrimal sac, the canaliculus, and other parts of the lacrimal passages is reported by L. P. Guy.<sup>38</sup> This condition was present since birth in a girl, 10 years of age. An artificial lacrimal passage, similar to a dacryocystorhinostomy, was created and a mucous membrane graft from the lip stitched to a hollow 2 mm. rubber catheter was so placed that the graft lined the passage. One end of the tube extended through the nostril and the other through the site of the lower punctum. The tube was removed on the sixth day. The passage was found still patent and functioning two years later.

## Lacrimal Puncta

**Congenital Absence**—Congenital absence of the lacrimal puncta in three members of a family, a father and two siblings, is reported by A. E. Town.<sup>39</sup> Excision of the lacrimal sacs was performed to relieve the dacryocystitis which developed in these cases. Only 21 cases of this rare condition have been reported previously and its occurrence in more than one member of a family has never been reported.

## Lens

**Abscess—Treatment**—A case of abscess of the crystalline lens which was treated by *chemotherapy* and *paracentesis* is reported by R. O. Rychener and E. C. Ellet.<sup>40</sup> As a result of this treatment, the infection was alleviated and the eyeball was retained. Chemotherapy and fever therapy are suggested for all perforating injuries of the eyeball. The effectiveness of repeated paracentesis in

cases of abscess of the anterior segment of the eyeball is attributed to the induction of increased concentration of the chemotherapeutic agent in the aqueous and an increased titer of the specific antibodies.

**Cataract Extraction**—According to C. S. O'Brien,<sup>41</sup> a keratome and scissors incision for cataract extraction is simpler and safer than the Graefe-knife incision. Moreover, the resultant astigmatism in 110 consecutive extractions averaged 1.64 D. in the former, while with the Graefe-knife incisions the astigmatism averaged 2.42 D.

**Following Filtering Operation**—A method of cataract extraction from the temporal side of the eye for cases in which a filtering operation had been performed previously for relief of glaucoma is presented by S. R. Gifford.<sup>42</sup> The corneal section is made with a knife approximately at 11 to 5 o'clock on the right eye or at 1 to 7 o'clock on the left eye. If necessary, the wound is enlarged with scissors to occupy a full half section without including the bleb. A conjunctival flap is prepared with scissors and corneoscleral sutures are inserted. A complete iridectomy is made only if a peripheral iridectomy has been performed previously. If a complete iridectomy had been made above during the trephine or if an iridencleisis with inclusion of the pillar of the iris had been made the temporal side of the coloboma is grasped with iris forceps and the iridectomy is enlarged. Enlargement permits grasping the equator of the lens with Verhoeff's forceps, which, in conjunction with the application of pressure at the nasal limbus by means of a ring expressor, effects delivery of the lens with its temporal border presenting first. This procedure was performed successfully in seven cases in which a filtering operation had been performed previously.

**Lancaster Technic**—K. L. Roper<sup>43</sup> describes the Lancaster technic of cataract extraction. Preliminary treatment and anesthesia are important. A small conjunctival flap is turned down on the limbus around the entire upper half of the eye. Three corneoscleral sutures are placed in solid corneal and scleral tissue (not in loose, yielding conjunctiva) before the section is made. The sutures pass through, not over the lips of the wound. An incision or groove is made along the line of the contemplated section at the base of the conjunctival flap by means of a guarded scleral knife part way through the sclera. Three sutures, equidistant from each other, are inserted. The anterior chamber is entered with an angular keratome and the section completed with scissors. The sutures are not tied until after intracapsular extraction by Kalt forceps. A basal buttonhole iridectomy is performed. The sutures are tied. *Eserine* is instilled. At the first dressing 48 hours later, *atropine* may or may not be instilled. A bilateral dressing is applied and a stiff Ring mask applied. *Aspirin*, *nembutal*, or *codeine* may be given postoperatively. Sutures are removed between the tenth and twelfth days. Intracapsular extractions by this method were attempted in 27 cases; extracapsular extractions resulted in only four.

### Motor Function

**Stimulation of Convergence**—The following exercises are advocated by W. R. Mathewson<sup>44</sup> for developing power of convergence: In a trial frame place prisms of successively increasing strength base out before the patient's eyes while he fixes a light at 6 M.; direct him to alternately approach to within 1 M. of the light and withdraw to 6 M.; and then with the prisms placed base out raise and lower the frame while he

attempts to fuse into a single light the two lights that he sees. Prisms base out may also be worn at home to stimulate convergence. (COMMENT: It is more convenient and equally efficacious to use a prism rack.)

## Muscles

### Convergence and General Health—

The relation of the convergence function to the general health of the patient as evidenced by his basal metabolic rate is described by S. V. Abraham.<sup>45</sup> He found that patients with subnormal convergence reserve power, in 83 per cent of cases have a subnormal basal metabolic rate. He concludes that in these cases correction of the minor errors of refraction and periodic orthoptic training are only palliative.

**Resection and Advancement of the Inferior Oblique**—Resection (with advancement) of the inferior oblique muscle at its scleral insertion for the correction of hypotropia and the improvement of cyclotropia which results from under action of the inferior oblique is advocated by C. Berens and M. Loutfallah.<sup>46</sup> The scleral insertion may be approached either below or above the tendon of the lateral rectus muscle. They report a case of paresis of the inferior oblique muscle with left hypotropia of 20<sup>Δ</sup> in the primary position associated with esotropia, 8<sup>Δ</sup> of incyclotropia and pseudoptosis of 2 mm. in which several previous operations had been performed. Post-operatively, the pseudoptosis was corrected. There was a right hypertropia of 8<sup>Δ</sup>, a residual esotropia of 22<sup>Δ</sup>, and incyclotropia of 4°. Because the right hypertropia seems to be increasing, retroplacement of the right superior rectus is contemplated. There is no rule for evaluating the requisite amount of resection of the inferior oblique.

**Orthoptic Training**—J. E. Lancaster<sup>47</sup> regards orthoptic training as an education in muscular coördination for the development of binocular skill. Orthoptics is interpreted not as an exercise of the ocular muscles or as a straightening of the eyes, but as an education in the use of two eyes together habitually to obtain comfortable binocular vision. In other words, training teaches skill in using an unskilled neuromuscular coördination.

**Strabismus — Measurement** — A discussion of objective strabismometry in young children is made by M. C. Wheeler.<sup>48</sup> He points out that the Hirschberg angular measure test is the best test for measuring the deviation in strabismus of young children, although in two-thirds of his series of cases higher readings were usually obtained with the screen test.

### *Surgical Treatment of Paralysis*—

B. F. Payne<sup>49</sup> describes an operation for the correction of strabismus in cases of paralysis of the lateral rectus muscle. The operation consists of resection of the medial rectus muscle, transplantation of the temporal halves of the tendons of the vertical recti muscles, and advancement of the lateral rectus muscle. The operation is performed in two stages, the operation on the medial rectus preceding the other by one month. The medial rectus is fixed directly to the superficial parts of the sclera with 000 chromic catgut sutures. The temporal halves of the tendons of the superior and inferior recti muscles are separated close to their insertion and their fibers are divided 15 to 20 mm. posteriorly. The lateral rectus muscle is divided vertically 8 mm. from its insertion and the stump is split in half toward its insertion. The tongues from the vertical muscles are united with those from the lateral muscles. The lateral rectus is then advanced and fixed

over the previous parts to the original insertion. Two cases were treated successfully in this manner.

**Treatment**—The therapeutic use of *prisms* is discussed by G. P. Guibor.<sup>50</sup> In divergence paralysis to develop fusion and fusion amplitude, fitover prisms base out may be worn and gradually reduced over a period of several months.

A case of concomitant esotropia which can be corrected by 25 $\Delta$  base out presents the following possibilities: (a) Correction of the total deviation by prisms. (Wearing the full amount of prism stimulates binocular single vision but rarely improves the deviation unless gradual reduction of prisms to undercorrect the squint is instituted.) (b) Overcorrection of the deviation by prisms. (Overcorrection is ineffectual in treating the deviation. The deviation should be measured by the screen test, not by the Maddox rod, which yields a higher reading.) (c) Undercorrection of the deviation by prisms. (The manifest deviation is not diagnosed by alternately covering the eyes, while prisms base out are used [total deviation] but by placing prisms over one eye, and occluding the fellow eye until the esotropic eye no longer moves temporally to fix. The deviation may also be measured with prisms, base out, using a red glass and reduced by 3 $\Delta$  to 5 $\Delta$  to be worn in loose fit-overs. By this means esotropia is frequently decreased and may even disappear.)

In paralysis of the lateral rectus muscle, resulting in esotropia, a prism base out just strong enough to overcome diplopia less 10 $\Delta$  should be worn before the paralytic eye and the nonparalytic eye should be occluded to make the paralytic eye fix. After a week the occluder is removed and diplopia recurs. If the paralytic eye suppresses, the nonparalytic eye is occluded for a half day every day

for an additional two weeks. The prism before the paralytic eye is reduced and that before the nonparalytic eye increased until the lesser amount of prism is used before the paralytic eye. As a result of this procedure, the amount of deviation usually decreases.

### Optic Nerve

**Coloboma**—A case of coloboma of the optic nerve characterized by a large disk, deep excavation, bluish-gray color, well-defined peripheral whitish margins and characteristic arrangement of the vessels is described by T. Steinberg.<sup>51</sup> Coloboma of the optic nerve unassociated with defects of the surrounding choroid is rare. Only 50 similar cases have been reported in the literature.

### Orbit

**Hemangioma**—The surgical removal of a hemangioma from the orbit of a soldier, 30 years of age, is reported by T. Crawford, E. F. King, and H. W. Rodgers.<sup>52</sup> The patient presented a progressive exophthalmos of the right eye, numbness, and neuralgic pain. Roentgen-ray examination was not informative. After osteoplastic resection of the outer wall of the orbit, a dark red irregular-shaped tumor was isolated and removed. Examination revealed that it was a mixed capillary and cavernous hemangioma. The iris, ciliary body, and lateral rectus muscle were injured but the visual acuity and the position of the eyeball returned to normal.

### Refraction

**Anisocycloplegia**—The term anisocycloplegia is applied by S. J. Beach<sup>53</sup> to a condition in which the accommodation of one eye is affected less completely than the other by a cycloplegic. The method of administration does not appreciably alter the response. The presence of this condition may be misleading

in cases in which glasses are prescribed directly from the cycloplegic or retinoscopic findings.

### Retina

**Angiomatosis**—J. S. Guyton and F. H. McGovern<sup>54</sup> obtained gratifying results in one case of bilateral angiomatosis of the retina and in one case of juvenile Coat's disease by diathermy coagulation. The angiomatous masses in both eyes of the first case were converted into scar tissue and the size of the dilated retinal vessels was reduced. Vision was retained in one eye and the appearance of the fundus of the other eye was improved. In the case of early juvenile Coat's disease of one eye and blindness of the other as a result of massive exudative retinitis, a primary peripheral retinal lesion in the seeing eye was obliterated with *diathermy punctures*. The lesion was converted into scar tissue and vision was preserved.

Obliteration of the lesion in a case of angiomatosis of the retina by diathermy was first reported by Weve in 1939. In 1941, Kaye reported successful results by electrolysis, surface diathermy, and diathermy puncture in two cases operated on by Stallard. In 1942 Lewis reported successful treatment by diathermy punctures.

**Treatment**—The treatment of angiomatosis of the retina (three eyes) by *x-ray irradiation* is reported by F. C. Cordes and O. C. Dickson.<sup>55</sup> Angiomatosis (von Hippel's disease) is a relatively rare condition—only 160 cases have been reported in the literature. In one of their patients, after treatment of an early lesion, marked improvement with retention of 0.8 vision for three and one-half years was obtained. In another patient an early lesion was present in one eye and a well-advanced lesion in the other eye. In this patient irradiation

of both eyes by 1800 r resulted in improvement of the early lesion with resultant visual acuity of 1.0, two years after irradiation, and deterioration and amaurosis of the other eye associated with detachment of the retina and gliosis.

Cordes and Dickson conclude that in early cases x-ray therapy is helpful; tolerance to irradiation increases with the age of the patient; and that advanced lesions do not respond to any type of therapy.

Although irradiation of the eye may result in cataract formation, this complication should not be considered too seriously, not only because the cataract can be extracted but also because this complication is rare—only 34 cases of postirradiation cataract up to and including 1932 have been reported in the literature.

**Detachment**—H. S. Gradle<sup>56</sup> discusses detachment of the retina. He states that before the age of 25 years detachment of the macular area is not usually followed by cystic degeneration but that in older adults if the macular area has been detached for more than a week cystic formation usually appears. He stresses the importance of juxtaposition of the retina and choroid while post-operative scars are forming by thorough drainage of the subretinal space by means of a sufficiently large hole in the sclera, an opening that will stay open for at least three days. After operation, the patient should be hospitalized for 14 days, moderate freedom permitted at home for another four weeks, and finally return to a sedentary occupation three months after the operation. Spectacles with a 3 or 4 mm. aperture are worn for at least two months; the size of the aperture is then increased every three weeks until the diameter is 1.5 cm. The spectacles are worn for five to six months after operation.

**Glioma**—Four cases of glioma of the retina in successive generations are described by W. L. Benedict and E. M. Parkhill.<sup>57</sup> These cases illustrate the hereditary nature of the condition. Clinical diagnosis was confirmed in all cases by microscopic examination. In case 1, the mother of the patient had a glioma of one eye at the age of seven months. The patients in cases 2 and 3 were twin sisters and the patient in case 3 gave birth to a daughter (case 4) who had bilateral glioma of the retina at the age of 28 months.

**Hemorrhages** — Five fatal cases of spontaneous nontraumatic subarachnoid hemorrhage are described by A. J. Ballantyne.<sup>58</sup> He discusses the mode of development of the hemorrhages in the eye. Hemorrhage results from rupture of an aneurysm or of a weakened vessel wall in the circle of Willis. Pain, paresis of the ocular muscles, and signs suggestive of cerebral compression and of meningeal irritation may be present. The presence of blood in the cerebrospinal fluid is diagnostic. Multiple hemorrhages occur independently and simultaneously at many places. Hemorrhages in the retina and vitreous occur as a result of sudden rise of intracranial pressure causing stasis in the venous channels which drain the eye and the orbital contents. Hemorrhages in the midbrain are responsible for such manifestations as oculomotor paresis and disturbances of the conjugate movements of the eyes.

**Macula — Amaurotic Idiocy** — R. Wyburn-Mason<sup>59</sup> reports 27 cases of amaurotic idiocy. Two distinct types are described which are unrelated except for their similar histologic appearance. The infantile type occurs in the Jewish race before the age of three years and it is fatal. As in Niemann-Pick's disease, lipid changes occur in the liver and the spleen and increased lipoids are present

in the blood. The juvenile type usually occurs in non-Jews between the ages of six and eight years and may present optic atrophy instead of degeneration of the macula, the final picture resembling retinitis pigmentosa. Moreover, this type is not associated with Niemann-Pick's disease.

**Hole**—A case of "hole" at the macula which resulted from looking for enemy planes in the direction of the sun is reported by C. A. Pittar.<sup>60</sup> The condition was present in a seaman, 26 years of age, who complained of defective vision for ten months. Examination revealed visual acuity of 2/60, a small nebula of the cornea and a hole at the macula associated with an absolute central scotoma.

**Internal Limiting Membrane** — Thickening of the internal limiting membrane at the macula was observed subjectively by E. G. Hill.<sup>61</sup> Ophthalmoscopically, a shimmering area in the region of the macula was observed. The symptoms were attributed to displacement of retinal elements, bleaching of the visual purple and lack of rigidity of the posterior part of the eye. He noted the following: Distortion of images, a shadowy veil, an "after-flash," and a disturbance in brightness when the eyeball was moved rapidly or when excessive convergence was performed. Visual acuity was not reduced. The lesion was attributed to exposure to intensive radiation for a period of many years which was transmitted freely in the infrared region.

**Neoplasm — Transillumination** — In a discussion of transillumination of the eye, R. I. Lloyd<sup>62</sup> points out that this test is of little value except for tumors situated anterior to the equator. Unfortunately, neoplasms occur much less frequently anterior to than posterior to the equator. Lesions for which transillumination is usually performed include

neoplasms, tuberculous masses, organized exudates, Coat's and von Hippel's disease, detached retina associated with underlying tumor, and extravasation of blood beneath the retina or choroid. Transillumination in pseudoglioma reveals that the tissue on the posterior surface of the lens is thin and translucent and that the eyeball behind the lens is not opaque. The use of the Hertzell illuminator introduced far back in the mouth in conjunction with the use of a mask to cover the entire face with the exception of the eyes is recommended for transillumination of the posterior part of the eyeball. Both pupils become visible through openings in the mask so that the two sides can be compared. Moreover, by this method of transillumination, the fundus can be examined ophthalmoscopically without its own light. The Lancaster or the Zeiss transilluminator is useful for retroillumination of the eye after the conjunctiva and Tenon's capsule are incised. Retroillumination should be performed routinely at the time of operation in every case of detachment of the retina.

### Thrombosis of the Cavernous Sinus

**Treatment**—In a summary of 58 cases of thrombophlebitis of the cavernous sinus reported in the literature in which recovery occurred as a result of expectant treatment with *bacteriophage* and *sulfonamide compounds*, W. J. MacNeal, F. C. Frisbee, and A. Blevins<sup>63</sup> point out that the cavernous sinus is more complex than the lateral and sigmoid sinuses. The former consists of venous channels and a meshwork of endothelial-lined tissue in association with a large artery and several nerves. The cavernous sinus may be affected by extension of an obturating thrombus along a communicating vessel, or by the formation of a clot in the sinus as a

result of local swelling secondary to infection of the ear, nose, paranasal sinuses, teeth, jaws, or by abscesses, carbuncles, or furuncles about the head or neck. The condition is usually fatal.

These authors report 45 cases of impending or well established septic obstruction of the cavernous sinus. Fourteen patients survived, 23 patients died within five days after bacteriophage was initiated, and eight patients died after 1 to 20 weeks. In other words, 31 per cent recovery rate is not much lower than that for an entire series of 500 patients with staphylococcemia. *Staphylococcus bacteriophage* is administered intravenously as follows: Increasing doses are given until a chill is obtained or until 500 to 1000 cc. have been given on the first day, then the bacteriophage is injected at least twice daily until the patient appears normal, then once daily for two weeks and once or twice a week for six months. *Sulfathiazole*, 8 to 12 Gm. (2 to 3 drachms), should be given on the first day and 1 to 8 Gm. (15 to 90 gr.) daily for 10 to 14 days. All facial furuncles should be treated conservatively and surgical procedures on the orbit, carotid artery, temporal bone, accessory sinuses, or intracranial structures should be undertaken with caution.

### Uveal Tract

**Undulant Fever**—J. Green<sup>64</sup> is of the opinion that undulant fever (brucellosis) is the etiologic factor of many inflammatory ocular diseases. He reports a case of severe kerato-iritis, characterized by plastic iritis, vascular keratitis, posterior synechiae, iris bombé, and secondary glaucoma of both eyes in a young woman. The following therapy failed to check the course of the disease: *Tuberculin, typhoid-paratyphoid, heat, blood transfusion, neoarsphenamine, gold salts, ultraviolet ray, sul-*



*fanilamide, thyroid, riboflavin, mydriatics, miotics, short-wave diathermy, and radium.* A diagnosis of brucellosis was made on a positive skin and opsonocytophagic test. Administration of *Foshay vaccine* resulted in clearing of both corneas. Optical *iridectomy* and *cyclodialysis* reduced the tension and improved vision of one eye. *Transfixion* and *iridectomy* reduced the tension but did not improve vision in the other eye. Green concludes that in the absence of other etiologic factors, tests for brucellosis should be made in all chronic inflammatory conditions of the cornea, iris, ciliary body, and uveal tract, especially early in the course of the disease and that prompt treatment with vaccine should be instituted to control the disease.

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# OTORHINOLARYNGOLOGY

*Edited by* FRANCIS L. LEDERER, M.D., and A. R. HOLLENDER, M.D.

## General Considerations

### Intrathecal Penicillin Therapy —

While considerable progress has been made in combating intracranial infections with the *sulfonamides*, an even brighter outlook seems in store when the drug, penicillin, becomes available for wider utilization. In a recent investigation of the treatment of experimental staphylococcic meningitis, the intrathecal administration of *penicillin* was employed by Pilcher and Meacham.<sup>1</sup> They found that intravenous treatment has little if any beneficial effect, but when the penicillin was injected intrathecally, even in relatively large doses, it produced a pleiocytosis in the cerebrospinal fluid, but no other significant toxic effect. Intrathecal treatment of experimental staphylococcic meningitis with relatively small doses of penicillin greatly reduced the mortality rate (from 93 per cent in control experiments to 54 per cent in treated animals). As a result of these studies, Pilcher and Meacham suggest that intrathecal penicillin therapy will probably be valuable in treatment of clinical staphylococcic meningitis.

**Headache:** The practical management of headache is discussed by Proetz<sup>2</sup> who endeavors to project the given case into one of the following classifications:

Having (A) Definite demonstrable causes; (B) semidemonstrable causes; (C) undemonstrable or only remotely suggestive causes.

Under the "A" grouping are included, first, local conditions such as demonstrable eye, ear, nose, brain and dental lesions; specific nerve affections such as trigeminal nerve pains and nasal ganglion syndromes; injuries, tumors, and infections. Under the same grouping are

included, second, definite remote conditions such as constipation and other digestive disturbances; organic diseases whose characteristic toxic or mechanical aberrations produce referred pains in the head; allergic conditions definitely traceable to known antigens; anemias; histamine poisoning.

Under the "B" grouping are migraine, psychoneurotic disturbances, fatigue and kindred relatively definite processes.

Under the "C" grouping come headaches which might once have been described as "idiopathic." They appear to be due to vascular changes.

It has been shown that extreme distention of the mucosal linings of the sinuses occurs without pain. Sinus infection does not necessarily mean sinus headache. The two may exist in one individual and be unrelated. It is important to remember that less than 5 per cent of headaches are referable to sinuses no matter what their location, and that the great majority are due to local vascular disturbances.

Proetz reminds us of the opinion of certain observers that when pressure changes occur in the vascular structures of the brain, the pain is likely to occur during the relaxation and dilatation which follow pressure, and not during the elevation of pressure.

The first step is the experimental alteration of the vascular tone. Unless there is hypertension, the patient is given *ephedrine* orally (together with *secobarbital* or some other barbiturate to minimize the unpleasant effects). Many headaches disappear promptly and many are controlled by this means alone. The ephedrine is given in doses of 0.0243 Gm. ( $\frac{3}{8}$  gr.) twice daily and if effective is

continued for one week. If, after the drug is withdrawn the headache returns, it may be resumed, but a long continued course of ephedrine is not recommended. Some persistent headaches can be controlled with occasional courses of ephedrine. If they are affected at all—even though increased—the suspicion of their vascular origin is confirmed.

Failing success with ephedrine therapy, **thyroid extract** is administered. Experience has shown that even when the basal metabolic rate is within normal limits or slightly increased, thyroid extract may still defeat the headache and cautious experimental administration is indicated. If this succeeds, the dosage is regulated by the symptomatology rather than by the metabolic rate.

The third experimental step consists in evacuating the lower bowel by enema. Headaches can be produced by some local retention or by the absorption of toxic products without demonstrable stasis. Abdominal discomfort is often coincident with the headache and has been described as of allergic origin.

Habitually recurring headaches, typically basilar and occipital, result from minor episodes of starvation, when too long a period is permitted to elapse between meals.

**Control of Hemorrhage**—The control of hemorrhage has always been a timely and important problem in otorhinolaryngology. Hulse<sup>3</sup> advocates the administration of **oxalic acid**, especially in inaccessible hemorrhage. The blood of human beings has been found normally to maintain a constant oxalic acid level. By the use of a trimetric method of testing the oxalic content of the blood, normal values have been established at 5.5 to 7.5 mg. per 100 cc. of blood. By the same method, blood values have been determined for conditions other than normal and in many cases an increase

in the blood coagulation time has been found to accompany a lowered oxalic concentration in the blood.

Chemically pure oxalic acid is made up in stock solution with distilled water, placed in stoppered bottles and autoclaved. One gram (15 gr.) of oxalic acid is added to 1 liter (34 fl. oz.) of distilled water. The acid is freely soluble in this dilution and is stable for some time. The injection of a few cubic centimeters of this solution into the human body is attended by a rapid and rather sustained fall in the coagulation time of the blood. The material has not been found to be toxic when administered properly and in no way endangers the status of the patient. The explanation of the action of oxalic acid in the body is not yet clear, but the fact that it lowers considerably the coagulation time has been established with certainty. Since this preparation lowers the coagulation time in normal persons, as well as those with certain abnormal conditions, it follows that it may be useful before as well as during and after operation. For the patient whose condition after operation would be endangered by any type of thrombosis this substance is obviously contraindicated.

As a prophylactic measure, 2 cc. (32 minims) may be given one to one-half hour prior to operation, followed by the same amount immediately afterward. In cases of profuse hemorrhage 3 (48) to 5 cc. (80 minims) may be given intravenously, followed in one-half hour by 2 cc. (32 minims) injected intramuscularly if the hemorrhage persists. Additional amounts of 2 cc. (32 minims) may be administered at hourly intervals if the hemorrhage does not stop, for three doses. Care should be taken to avoid the formation of a dense and tenacious clot in any of the air passages. Many of the distressing hemorrhages associated

with carotid blood vessels can be controlled or stopped by the judicious use of this solution, and its administration will, according to the author, often prevent surgical mayhem on this system.

## LARYNGOLOGY

**Voice Training for Laryngectomized Patients**—An interesting and valuable treatise on voice training for laryngectomized patients is presented by McCall.<sup>4</sup> He emphasizes the necessity for preoperative training and states that the esophageal voice is the result of timing and synchronization of movements of the lips, tongue, and teeth with an adequate expulsion of air from the esophagus and pharynx. Definite narrowing of the cricopharyngeal space after laryngectomy creates sound vibrations when a sufficient volume of air is expelled from the esophagus. Therefore, development of an esophageal voice is dependent on the patient's ability to expel forcibly an adequate volume of air from the esophagus, that is, the act of belching. The laryngectomized patient's ability to develop an esophageal voice is dependent on his ability to master the technic of belching. If he does not learn this, he will not develop an esophageal voice. It is much easier to learn to belch properly before the larynx is removed than afterward. If training is delayed until after the operation, the check to respiration offered by the glottic valve is gone, and the patient will explode air from the trachea instead of the esophagus.

The belching effort is acquired easily by some patients; others find it difficult. By training patients in this effort for a week or ten days before laryngectomy, the greatest difficulty in the development of an esophageal voice is overcome. Most patients who must submit to laryngectomy desire a few days to arrange their affairs, and if this time is utilized in

learning to belch, it will greatly shorten the postoperative period of training for the development of an esophageal voice. To aid the patient in learning to trap air in the esophagus, carbonated drinks are prescribed. The patient is told to inhale deeply and then cease active respiration while he eructates air from the stomach and esophagus.

As soon as the feeding tube is removed, postoperatively, the patient is required to resume the belching effort. At first a great deal more stress is placed on having the patient belch than on having him to try to form words. In the beginning, the patient is tempted to try to form sentences. This should be discouraged, for he should try one word at a time. When he has achieved the formation of single words, it is an easy matter to put phrases and sentences together.

Close coöperation and understanding between the surgeon and the patient in the preoperative and postoperative training period are required for the best results. It is insisted that the patient devote at least two or three hours a day to the effort to talk.

**Cancer of the Larynx**—Criteria for the selection of treatment of cancer of the larynx are comprehensively considered by Jackson and Blady.<sup>5</sup> They state that the major considerations in the selection of a method of treatment are, first, the prospect of cure of a fatal disease, and, second, conservation of function, in other words, voice. Among the secondary considerations are duration of morbidity, degree of discomfort, and possibility of complications.

The criteria for the selection of a method of treatment of cancer of the larynx are listed as follows: (1) The presence or absence of cervical metastases; (2) the location and extent of the lesion, as evidenced by its appearance on

direct and indirect laryngoscopy and by lateral and planigraphic roentgenographic study; (3) the motility and mobility of the laryngeal structures; (4) the histologic character of the lesion, and (5) the general physical condition and temperament of the patient.

The indications for laryngofissure and laryngectomy are: (1) Lesions occupying the middle third of one vocal cord are suitable for laryngofissure by the "clipping" technic. (2) Lesions reaching the anterior commissure and even involving the opposite cord are also amenable to extirpation by the laryngofissure route, but in such cases the "anterior commissure" technic should be used. (3) Lesions in which the growth is cordal but has reached the posterior end of the cord and produced impairment of motility, or has extended subglottically, ordinarily call for total laryngectomy. (4) Lesions in which the tumor has involved the cartilage (but not the muscles) also call for laryngectomy, provided there are no metastases.

The indications for irradiation are: (1) "Inoperable" growths which are extrinsic by origin or extension, or which have cervical metastases. The latter must be treated by protracted irradiation, followed immediately by implantation of radon, either through the skin or after surgical exposure. (2) Lesions which have reached the posterior extremity of the cord but have not produced impairment of motility of the cord. Such growths constitute a group for which laryngofissure is contraindicated but for which irradiation may be preferred to laryngectomy. It is the consensus at present that impairment of motility contraindicates laryngofissure, and while such impairment is not a contraindication to irradiation, it is not a favorable sign; complete fixation of one or both sides

of the larynx, on the other hand, is considered even less favorable.

**Paralysis of the Larynx**—A study of 270 cases of paralysis of the larynx was made by Luehs,<sup>6</sup> who classified the paralyzes into central and peripheral groups. The latter was further classified into: (1) Mechanical; (2) inflammatory; (3) tumors; (4) traumatic (surgical and nonsurgical trauma), and (5) idiopathic.

The tension of the affected cord, rather than its position, is the best index to the completeness of the paralysis. The immobile cord was more often in the median line than in the cadaveric position in this series. The voice cannot be relied upon as a criterion for the presence or absence of paralysis of the vocal cord, because when tension of the cord remains good, the voice is often normal. This occurs even in bilateral abductor paralysis.

Carcinoma, exclusive of the larynx, is the most frequent single cause of unilateral paralysis of the vocal cords. Thyroidectomy is the most common cause of bilateral abductor paralysis. In the author's series, preoperative paralysis was exceedingly rare. It is emphasized that the larynx should be examined routinely before and after thyroidectomy.

Complete paralysis, with loss of tension of the cord, is most frequently seen in infiltrating lesions such as carcinoma of the esophagus, lungs, trachea, thyroid gland, etc., and in conditions producing prolonged mechanical pressure or stretching as is exerted by an aneurysm. The paralysis is usually of the incomplete abductor type when the nerve has been injured suddenly, as in thyroidectomy. This has not been satisfactorily explained.

The left recurrent nerve is seemingly more susceptible to injury than the right, even when intrathoracic diseases are ex-

cluded. The prognosis for recovery of function of the cord is poor, regardless of cause, but is best in those cases where no cause for the paralysis can be demonstrated.

**Acute Laryngotracheobronchitis**—A treatment of the obstructive edema of acute laryngotracheobronchitis is described by Baum.<sup>7</sup> He employs *concentrated plasma* to reduce the edema of the subglottic tissues and tracheobronchial mucous membrane. This treatment is not intended, however, as a cure for the infection itself. It is the osmotic action of the hypertonic plasma protein introduced into the blood stream which accomplishes the objective, and that objective is the withdrawal into the blood stream of the fluid of edema in the interstitial tissue spaces of the subglottic area and in the mucosa and submucosa of the tracheobronchial tree.

Instead of restoring the desiccated plasma with the full amount of water (usually 250 cc.), Baum restores it with about 60 cc., thus making approximately a one-fourth dilution. The exact concentration is not important so long as the plasma is all restored, without any dry lumps and not too thick to pass through an intravenous needle. It is often wise to make use of the *humidified oxygen tent* until the plasma is prepared. In the more serious situations, gentle *laryngeal suction* through the direct speculum, followed by the oxygen tent, should be utilized. If danger is imminent, temporary *direct intubation* may be used. Even if tracheotomy has already been done, the intravenous treatment should be given just the same, since there are a number of advantages in its administration.

From 25 to 40 cc. of the four times concentrated plasma is usually administered, depending on the size of the child and the severity of the case. Reactions

resulting are rare. If a considerable dosage of hypertonic plasma is to be given, especially if there is any suspicion of circulatory embarrassment, it is desirable to withdraw a moderate amount of blood. The amount should be three or four times the quantity of concentrated plasma to be administered. The results of this treatment have been very encouraging. The disappearance of obstructive symptoms does not indicate that the actual infection is cured; however, the vital respiratory function is relieved, and there remains only a relatively simple non-obstructive inflammation to be dealt with. The method described is applicable to other types of laryngeal or tracheobronchial edema.

**Myasthenia Laryngis** — Myasthenia laryngis is the name given by Jackson to a symptom complex involving the phonatory mechanism of the larynx. It appears to be a pathophysiologic condition rather than one demonstrable by anatomic changes.

The symptoms are dysfunction of the larynx, hoarseness, weakness of the voice, and the feeling of tightness or spasm in the throat. In nonsingers, besides the complaint of hoarseness and weak voice, the chief phenomenon is spasm of the larynx during eating or drinking, occasionally followed by dysphonia. Jackson states that this condition results from involvement and fatigue of the thyroarytenoid muscles, and that it undoubtedly accounts for the ruination of the throats of many singers, clergymen, public speakers, and actors.

In eight cases treatment<sup>8</sup> consisted of intramuscular injection of *prostigmin methylsulfate* (1:2000) three times weekly for the first week, and twice weekly thereafter. *Prostigmin bromide*, 15 mg. three times daily, was administered orally in addition to the injections. Those patients who were not in the best

physical condition were also given a course in vitamin B Complex.

Seven of the cases were successfully treated with the medication described.

A close relationship between myasthenia laryngis and gravis is postulated.

**Hereditary Hemorrhagic Telangiectasia**—It is Figi and Watkins'<sup>9</sup> opinion that hereditary hemorrhagic telangiectasia (Rendu-Osler's disease) is a condition with which laryngologists should be more acquainted, since the vascular lesions characteristic of it occur most frequently in the nasal and oral mucous membranes. Here they often give rise to severe and at times fatal hemorrhage. During the past twenty years, 20 cases of this disease have been recognized at the Mayo Clinic. None of the patients were blood relations. Twelve of them were males, eight were females. They ranged in age from 25 to 67 years and three-fourths of them were between 30 and 60 years of age.

From the standpoint of diagnosis, hemophilia, purpura haemorrhagica, aplastic anemia, and acute leukemia must be considered. The laboratory findings are usually characteristic and aid in differentiating these blood conditions. In hereditary hemorrhagic telangiectasia, the blood coagulation factors are within normal limits, the telangiectases are most frequently seen on the face, neck, and trunk; are bright in color, often elevated and tend to fade partially on pressure.

For immediate control of hemorrhage by the patient, the most useful device is the ingenious modification of the **Cooper-Rose inflating plug** devised by Hurst and Plummer. This consists of a finger cot placed over the end of a small catheter and tied snugly with fine thread. This is kept continuously at hand by the patient so that when active bleeding occurs it can be lubricated, inserted well back

in the nostril, and inflated either by placing the open end of the catheter in the mouth or by a rubber bulb. Firm uniform pressure is thus applied to the entire interior of the nasal fossa and will usually effectively control the bleeding for the time being. After the hemorrhage has stopped, the cot is slowly deflated and withdrawn or allowed to drop out of the nostril.

For more lasting effect, **radium**, **actual cautery**, **electrocoagulation**, and various chemical caustics, including **chromic acid**, **trichloroacetic acid**, and others, have been employed. In the hands of the authors, electrocoagulation has given better results than any other form of therapy. In a few instances general anesthesia has been necessary. For this purpose **pentothal sodium** has been administered intravenously. The coagulation requires extreme patience, persistence, and gentleness. In view of the intensive electrocoagulation required in some of these cases, it is difficult to conceive of chromic acid or other similar chemical caustics effectively controlling the bleeding. On a number of occasions it has been necessary to use diathermy persistently for one and a half or two hours at a single sitting except for periods of intermittent cocaineization, but the ultimate results have well repaid the effort.

About the lips, the oral cavity, and on the cutaneous surface of the body, the electrocoagulation has proved even more satisfactory in eradicating the angiomas than in the nasal fossae.

The use of radium in treating this condition is, in the opinion of the authors, contraindicated. **Transfusions** of citrated blood are often essential in combating the secondary anemia associated with this condition, but they exert no curative effect. **Snake venom** proved to be of little benefit in the cases reported.



**Androgen Therapy**—The effect of androgen therapy on the voice and vocal cords of adult women is discussed by Goldman and Salmon.<sup>10</sup> Observations were made from a series of over 400 patients who were treated with various androgens, *viz.*, *testosterone propionate* administered intramuscularly, *methyl testosterone* orally, *testosterone* by implantation of pellets, and *testosterone in solution in propylene glycol* sublingually. The series comprised cases of dysmenorrhea, menometrorrhagia, premenstrual tension, and menopause syndrome. The patients varied in age from 16 to 61 years. In this report, the observations were recorded in 23 cases that manifested striking vocal and laryngeal changes as a result of the intramuscular administration of testosterone propionate. The total amount of testosterone propionate which these patients received varied from 225 to 3000 mg. over periods extending from 1 to 22 months, given in individual doses of 25 to 50 mg. two or three times weekly.

Persistence of vocal disturbance and physical alteration of the vocal cords existed for varying periods of time up to two and one-half years after discontinuance of androgen therapy in 11 cases.

This study suggests that there is a striking similarity between the vocal and laryngeal changes in women who receive androgen therapy and the physiologic development of the voice and larynx in boys at puberty.

In order to avoid the production of vocal and laryngeal changes in women receiving androgen therapy, the dose must be kept below the threshold for these phenomena. For the average woman, this threshold is approximately 500 mg. of testosterone propionate per month. The therapeutic dose of 200 mg. per month recommended makes it possible to utilize the valuable therapeutic

properties of testosterone propionate without running the risk of causing laryngeal complications. As an additional safeguard against androgen overdosage in susceptible individuals, it is recommended that weekly vaginal smears be taken and that therapy be discontinued if the androgen effects appear in the smear.

## OTOLOGY

**Otogenic Complications**—Early otogenic complications are evaluated by B. Woodson,<sup>11</sup> who cites several case reports to illustrate various aspects of certain otogenic complications. Persistent pain following the incision of an eardrum may indicate the onset of a severe fulminating infection. A fulminating otitis without pain occasionally occurs. The absence of pain in an ear in the presence of obliterated landmarks of the tympanic membrane gives the danger signal for early adequate therapy where a delay may be disastrous. While *mastoidectomy* may not preserve and restore hearing, the removal of the chronic suppurative otitis media at least removes a definite major cause for not only a gradual loss of hearing but also a constant focus for a serious, if not fatal, intracranial complication. The conclusion of the author is that early surgery is indicated in the presence of a gradual loss of hearing accompanying a chronic suppurating otitis media.

**Chronic Otorrhea**—In the opinion of Emerson and Dowdy,<sup>12</sup> certain cases of chronic otorrhea can be controlled by treatment of the eustachian openings with radium. Improvement was noted in children treated primarily for eustachian adenoids and deafness but who, at the same time, suffered from chronic otorrhea attributable to the hypertrophied lymphoid tissue in and about the eustachian orifices.

While different technics no doubt are applicable, the authors employed 25 mg. (two 12.5 mg. needles) of *radium*. Each needle is composed of an alloy having a density of 8.7 and walls of 0.3 mm. thick, transmitting 99.2 per cent of gamma rays. A relatively high percentage of the radiation is beta radiation. The only filtration is that provided by the walls of the needles. Approximately one-third of an erythema dose (5 mg. hours) should be sufficient. This requires an exposure time of 12 minutes to each eustachian tube orifice; both sides may be treated at once. *Pontocaine*, 2 per cent, is used for anesthesia.

No claim is made that this method is a cure or a panacea for chronic otorrhea. And it is properly stressed that its recurrence is to be expected.

**Tinnitus**—Fowler<sup>13</sup> states that if one disregards the auditory hallucinations occurring in organic diseases of the brain and in the psychoses, there are two kinds of tinnitus: (1) Vibratory, caused by actual autogenous vibrations reaching the ear from any part of the body, and (2) nonvibratory, caused by biochemical irritation of the auditory neural mechanism. Either of these two kinds of tinnitus may be superimposed on the other, in which case either one with sufficient intensity and proper frequency can diminish or increase the loudness and change the timber and therefore the degree of annoyance of the other. The successful treatment of the diseases or disorders causing deafness depends on the recognition of these distinctions. Any treatment that claims to be just for tinnitus or deafness is on its face unscientific.

The following conditions are commonly associated with the illusion of sound called nonvibratory tinnitus: (1) Impacted cerumen; (2) pathologic closure of the eustachian tube; (3) acoustic

trauma; (4) otitis media and otosclerosis; (5) drugs and poisons; (6) cardiovascular disorders; (7) gastrointestinal disorders; (8) psychoneurologic disturbances; (9) allergy; (10) idiosyncrasy; (11) involvement of otic, gasserian, and geniculate ganglions, and (12) intracranial growths.

Tinnitus from any cause is best treated by removing the cause, but this is often impossible, because not only does nonvibratory tinnitus vary on such slight alterations in the local environment of the ear and even of the body that the cause is not detectable, but the lesion is often permanent. The neural elements remaining under constant stress or irritation then usually continue to produce tinnitus intermittently or constantly.

The loudness of the tinnitus and the disagreeableness of its timber is underestimated by some persons and overestimated by others. The degree of exaggeration can be determined to some extent by measuring the loudness and timber of the tinnitus. In the treatment of tinnitus brought on by autonomic nervous system episodes, Fowler suggests that the patient be given 2 or 3 tablets of *glyceryl trinitrate* (0.65 mg. [ $\frac{1}{100}$  gr.]) with the instruction to take one immediately when he senses the aura or actually hears the tinnitus returning or increasing in volume. A favorable effect usually follows. This may be due to the drug but the psychological factor is important and may be equally, if not more, responsible in aborting the attacks. In older persons with cardiovascular disorders, treatment along similar lines is often indicated, because it may benefit these disorders as well as the tinnitus.

If the tinnitus cannot be eliminated, efforts should be made to lessen its annoyance by rehabilitation of the patient to a more normal and social status. Lip reading and hearing aids may prove

beneficial. Often the deafness as well as the tinnitus is lessened. Finally, it is emphasized that tinnitus is something more than a disorder of hearing.

### Deafness

**Benzyl Cinnamate Therapy of Deafness**—The effect of *benzyl cinnamate* on certain forms of deafness is reported on by Jacobson.<sup>14</sup> Forty-five patients were treated with intramuscular injections of a solution of benzyl cinnamate from January to August, 1942. All of them had been treated for a long time previously by the well-known classic method but without results. In addition to being hard of hearing, a great number of them were affected with dizziness and tinnitus.

The patient receives one intramuscular injection of 0.33 to 1 cc. (5 to 15 minims) of a 3.2 per cent solution of benzyl cinnamate for a period of 12 days. He is then allowed a period of rest of 10 to 15 days. Thereafter, the injections are resumed, and after the third series of injections, the patient is given one month's rest. The same cycle may be repeated after an interval of about two months.

Of the 45 patients to whom a questionnaire was sent, 32 answered. Seventeen of these 32 stated that they had improved. Of 24 who complained of tinnitus, two patients reported its disappearance, seven stated that tinnitus was diminished in intensity, while 15 noted no change in this symptom. Of the 32 patients, nine complained at the same time of dizziness. Three patients reported its disappearance, five stated that it was diminished, while one reported no change. Among the patients with dizziness a certain number were affected with Meniere's syndrome. Two patients who presented typical symptoms had been treated for several years without improvement. After

the first course of injections a satisfactory result was reported.

**Chronic Progressive Deafness**—It has always been known that there is a relationship between blockage of the eustachian tube and chronic progressive deafness. In fact, otologists now realize that chronic progressive deafness in adult life probably had its origin in some tubal or middle ear involvement earlier in life. The anatomic position of the pharyngeal orifice of the eustachian tube predisposes it to infections and involvement by conditions of the nose, sinuses, and lower part of the respiratory tract. The chief function of the eustachian tube is to equalize the air pressure of the tympanic cavity with that of the outside atmospheric pressure. The foregoing facts are reviewed by Decker<sup>15</sup> preparatory to describing the histopathology of the eustachian tube. In the main the mucous membrane in the cartilaginous portion was a high columnar ciliated type and in the bony portion a low columnar ciliated type. This author, as well as many others, calls attention to the finding in children of large hyperplastic lymphoid structures at the opening of the tube. Instead of atrophying, these structures may become hypertrophied and cause blocking. A tubal tonsil in the pharyngeal end of the tube is often present and may be considered a part of Waldeyer's ring. Among the causes of blockage of the eustachian tube, repeated attacks of rhinopharyngitis is the most common. Another important cause of tubal occlusion is hyperplasia of lymphoid tissue in the pharyngeal portion of the tube. While the adenoids in one way or another may obstruct the orifice of the tube, other causes include allergic swellings and anatomic defects of the nose, adhesions and scars about the opening, tumors, neoplasms, tuberculosis, diphtheria, and syphilis. Large crusts of atrophic rhini-

tis, paralysis of the facial nerve, paralysis of the levator veli palatine muscle, hypertrophy of the posterior lips of the turbinates, rhinoscleroma, septal exostosis, calcification, ossification of the cartilaginous tube, and malocclusion and overbite many times have a bearing on closure of the tube. The treatment of the acute process consists of improving ventilation of the tubes by the use of *shrinking solutions* to the orifice and the application of *antiseptics*. *General supportive treatment* is important. After the acute stage, removal of the cause is essential. For this purpose, the accepted procedures now are *surgical extirpation* of the hypertrophied lymphoid tissue, *roentgen ray*, and *radium radiation*. If an allergic factor is at fault, the causative agent should be determined, if possible, and *desensitization* performed. Anatomic defects, neoplasms, strictures, and other causes should be managed by appropriate recognized procedures.

**Hearing Impairment**—Kuhn<sup>16</sup> outlines the symptoms, diagnosis, and allergic findings of hearing impairment. Audiograms are presented to bear out the views expressed. In cases suspected of having hearing difficulties that are of an allergic basis, and who have had considerable improvement demonstrated in their hearing after avoiding or being hypersensitized to certain allergins, one is led to the conclusion that there is a definite pathological chain that results in interference in hearing, whatever the exact pathological picture may be. Concluding, Kuhn remarks: (1) There is an appreciable number of patients with lowered hearing due to an allergy. (2) The audiogram is changed in positive cases by giving adrenalin, and these positive cases are improved by allergic management. (3) There may be a combination of pathology with a superimposed allergy.

### Meniere's Syndrome

**Treatment — Histamine** — Atkinson<sup>17</sup> points out the reasons for the failure of any particular treatment to achieve its hoped-for results in Meniere's syndrome. One lies in the laxity of the diagnosis. The other reason is the tendency, partly unconscious, to regard the malady of Meniere as a disease *sui generis*. The tendency is to make the diagnosis on history and deafness alone, which is a dangerous practice, because only by the most thorough examination and a process of exclusion can accurate diagnosis be achieved. A neurologic and general as well as otologic examination is necessary. Cases of idiopathic Meniere's syndrome should be divided into two groups, those in which the patients are sensitive to *histamine* and those in which they are insensitive, according to their reaction to an intradermal test. The author condemns the indiscriminate use of histamine because in his experience relapse, and in several instances actual deterioration, occurred, more or less soon after the beginning of the treatment. It was a general experience that in such cases it was much more difficult to stabilize with *nicotinic acid* than in those in which histamine had not been given. Larger doses and more intensive and more prolonged treatment were required, and temporary setbacks, one or more, were almost the rule. A small group of patients who are sensitive to histamine will benefit from administration of the drug, but after the initial improvement actual harm may result to the majority group of persons who are insensitive to the drug. In the same way, nicotinic acid administered wrongly to the patients who are sensitive to histamine will increase symptoms. In judging results from any treatment, many extraneous or mitigating circumstances must be taken into account, since in a condition like

Meniere's syndrome, it is difficult to be both accurate and honest.

Several reports have appeared during the past few years on the use of histamine in the treatment of Meniere's syndrome. Since controversy still continues as to the value of this therapy, the experience of independent workers are of interest in that they may throw additional light on the subject. Rainey<sup>18</sup> treated 22 patients with Meniere's syndrome by means of *histamine phosphate* intravenously. Of these, 17 had striking results, while five failed to respond favorably.

Rainey described the technic which he employed as follows: 1 cc. (16 minims) of histamine phosphate 2.75 mg. is diluted in 250 cc. of isotonic solution of sodium chloride. This is given by the drop method 70 drops to the minute, after testing the patient's tolerance by giving 20 to 30 drops per minute for the first five minutes. The blood pressure is determined every ten minutes, since with most patients there is considerable variation.

It is fully realized that other methods of treatment have been helpful in relieving Meniere's syndrome and that some patients get well without treatment. Despite these facts, Rainey believes that in histamine therapy we now have the most promising means of correcting this difficult condition.

**Magnesium Salts**—There are few if any drugs which have been omitted in the endeavor to afford relief to patients with Meniere's syndrome. Now A. Schick<sup>19</sup> reports his experience with the use of *magnesium salts* in this condition. This treatment was prompted because it has proved definitely of value in migraine. Essentially the treatment consists of a series of intravenous injections of a magnesium salt solution. Five cubic centimeters (80 minims) of

a 50 per cent magnesium salt solution are given two or three times a week, from 10 to 20 injections altogether, depending on the response of the individual patient and the severity of the symptom-complex. Sometimes the treatment is repeated after a few months. The injection has to be administered at an extremely low rate with the patient in the recumbent position in order to decrease the sensation of heat which arises.

In many instances in which this therapy was employed, the results were striking. In favorable cases the seizures disappeared completely or grew milder and became less frequent.

The theoretical basis of the magnesium sulfate treatment of Meniere's syndrome has not yet been completely established. Two factors probably play a decisive rôle. One is the recognized effect on the central and peripheral nervous system, influencing the entire vasomotor system, especially in the vestibular apparatus. The other factor may be the diuretic action of magnesium salts, counteracting either the tendency to sodium or water retention or exudation into the labyrinthine spaces caused by the vasomotor disorders.

### Pharynx and Neck

**Lateral Pharyngitis**—According to Frickle and Pastore,<sup>20</sup> granular or hypertrophied lateral pharyngeal bands usually denote infection of the lymphoid tissue in the throat. When these structures are affected, the condition is usually called lateral pharyngitis. The lateral bands are linear patches of lymphoid tissue situated in the lateral portion of each side of the pharynx posterior to the pharyngeal palatine arch. The types described are finely granular, coarsely granular, and cryptic.

Because all infected tissue in Waldeyer's ring cannot be eliminated by op-

eration alone, compensatory hypertrophy occurs after operation. Numerous methods have failed to reduce this hypertrophy, a circumstance which led Frickle and Pastore to employ *radium radiation*.

For the treatment of infected pharyngeal bands, they have devised a simple applicator, which is a metal rod threaded at the end, so that a brass and silver tube containing radon can be attached. A hinge is inserted just proximal to the radon tube which can be locked at an angle of about 50 degrees. The rod is introduced through the nasal passage; on turning the rod, the hinged part drops down and the tube containing radon presses against the lateral wall of the pharynx. The dosage is varied from 1.5 to 4.5 Gm. minutes, but after the first few months of use of this method 3 Gm. minutes was found to give the best results. A 50 mc. tube is thus left in for one hour through each nasal passage to provide this dosage.

Of 24 patients treated, 20 had only one treatment and four had two treatments a few months apart. The results were successful in all cases. All patients are traced; 14 by letter and the remainder by return visits. All had fewer colds, less severe sore throats, and improved general health. Generally improvement was first noted one month after the treatment. There has been no reactions or injurious effects.

**Ludwig's Angina** — Williams and Guralnick<sup>21</sup> present a method of dealing with Ludwig's angina. They suggest: (1) Establishment of an adequate airway, by tracheotomy if necessary; (2) anesthesia by intravenously given pentothal sodium; (3) administration of sulfonamide drugs, locally and by the mouth, and (4) bacteriologic examination of exudate to determine the choice of postoperative dressing.

Diagnosis is made by recognition of the classical symptoms usually described in textbooks. *Tracheal intubation* is satisfactory in furnishing an adequate airway, but it may lead to serious problems, even death. *Tracheotomy* is preferable, especially if exposure of the trachea has been performed as a preliminary measure. Once the diagnosis has been made, drainage should be established promptly. In case of bilateral involvement, the opening should extend almost to the angle of the opposite jaw with exposure of the submaxillary and sublingual spaces, and if pus has dissected into the posterior parapharyngeal space, it should be opened as well. Five to 8 Gm. (75 to 120 gr.) of *sulfonamide* crystals are implanted into the wound which is loosely packed with *iodoform gauze*. If Vincent's organisms are present, *zinc peroxide dressings*, changed every four hours, often prove effective.

In the event complications are avoided, secondary closure of the wound should be feasible by the eighth day. The incision exposing the trachea may be closed on the third or fourth day, or whenever the need for tracheotomy has passed.

The oral administration of the *sulfonamides* (1 Gm. [15 gr.] every four hours) is recommended but only as a supplement to surgical drainage. *Oral hygiene* is important because a dental lesion was found to be the initiating factor in 90 per cent of 53 patients. The authors suggest a watery suspension of zinc peroxide powder before and after teeth extractions.

**Cricopharyngeal Spasm** — Because of the difficulty in differentiating between functional disturbances and organic diseases at the level of the cricopharyngeal muscle, Clerf and Putney<sup>22</sup> contend that a diagnosis of cricopharyngeal spasm should not be made until other diag-

nostic possibilities have been excluded by a thorough study, including esophagoscopy. Abnormal contraction or spasm in the cricopharyngeal region produces difficulty in swallowing and pain. While usually ascribed to functional disorders, there is actually a definite organic disease at the cricopharyngeal level. General anesthesia or profound narcosis during esophagoscopy examination will aid in differentiating between the normal and the spasmodically contracted or organically narrowed cricopharyngeus. Dysphagia, a common symptom of organic disease of the hypopharynx, esophagus, and certain disorders of the larynx and periesophageal structures, is also a manifestation of the tension associated with any of the neuroses. Thus, diagnosis of globus hystericus, esophageal neurosis, and hysterical dysphagia should be made only after the presence of organic disease has definitely been ruled out.

**Acute Tonsillitis**—Tamari and Berman<sup>23</sup> elaborate on the factors influencing the duration of acute tonsillitis. We are reminded that certain meteorological factors favor the incidence of acute infections of the throat and that there is a relationship of seasonal differences and meteorological factors to some respiratory diseases. A study of the upper respiratory diseases in children at the Cook County Hospital in Chicago showed that there is a sharp increase in the number of upper respiratory tract infections during July and August over that of May and June, a situation explainable on the basis of basal metabolism which is variable, increasing with the falling temperature and decreasing as the temperature rises. Coincident with the changes in metabolic rate is the ability of the body to produce immune bodies, which is high when there is an increased loss.

Other conditions which decrease the general resistance of the individual and

prolong the duration of acute tonsillitis are rickets in children, anemia, tuberculosis, and other debilitating diseases. In adult females, an acute attack of tonsillitis is prolonged and healing is much delayed during the menstrual period.

It has been shown that acute tonsillitis is characterized by a type of phlegmonous inflammation. While the normal healthy mouth contains a great many saprophytic pathogenic microorganisms of various types, the streptococci and pneumococci are mostly responsible for acute tonsillar infections. Local conditions extending an attack of acute tonsillitis are chronic infections of the teeth and mouth, chronic sinusitis, and chronic infectious diseases of the larynx, trachea, and bronchi.

There are numerous local factors which retard normal healing process of acute tonsillitis. The course is often prolonged if the infection is superimposed on tonsils having previous infective changes, or when cystic degeneration of the tonsillar tissues is present. Still another factor influencing the normal course of acute tonsillitis is incomplete *radium* or *x-ray therapy*, which is used for destroying adenoid tissue.

It appears clear that the normal reaction of the tonsil to an inflammation depends upon the state of the mucosa, the connective tissue, and the normal arrangement of the follicles. The normal defensive mechanism is destroyed in those cases in which (1) the mucosal lining loses its permeability, (2) the connective tissue fails to absorb the toxic material, and (3) the reticuloendothelial system is disarranged.

**Vincent's Infection**—Although numerous methods have been suggested for the treatment of Vincent's infection, especially that involving the tonsil, none has proved entirely satisfactory. The probability that the fusiform organisms



enter only tissues weakened by some other cause is considered by Linton,<sup>24</sup> who states, however, that this cause has not been definitely determined. Remarkable recoveries were observed when patients were placed under *sulfathiazole* therapy. In a small group of cases, there was definite improvement in soreness of the throat within 24 hours, with most symptoms gone in 48 hours, and practically complete clinical recovery within 72 hours under treatment with *sulfathiazole*.

The dosage and method of administration ultimately used consisted of a 0.5 Gm. (7.5 gr.) *sulfathiazole* tablet dissolved on the tongue every two hours during the day and 1 Gm. (15 gr.) dissolved on the tongue every four hours during the night. This was continued for two days, at which time the patient would voluntarily discontinue medication, unless directed otherwise, because symptoms had disappeared. When infection also was present about the gum margins, it was advised that the *sulfathiazole* tablet be moistened with a few drops of water to make a paste and this used to rub into the gum margins.

**Sulfa Therapy — *Sulfathiazole* —** The local use of *sulfathiazole* powder for acute pharyngeal infections is evaluated by Freeman.<sup>25</sup> The powder is applied to the laryngeal mucosa with a compressed air powder syringe. It should be applied until it thickly cakes the involved areas. Nasopharyngeal applications are made through the nose or with a shortened eustachian catheter, placed behind the soft palate. In the author's studies the dose was difficult to ascertain, varying between 1 and 2 Gm. (15 and 30 gr.) per treatment. The patient should avoid eating or drinking for two hours following treatment, during which no other form of therapy is employed.

The method rapidly produces subjective and objective relief and materially shortens the course of the disease. The possibility of systemic damage from the use of *sulfathiazole* is negligible with this method of treatment. It is inexpensive and easily carried out on ambulatory patients.

According to Fenton,<sup>26</sup> *sulfathiazole* seemed to him preferable for local use because of its slow solubility in tissue fluids; hence its action would seem to remain concentrated at the area of administration for somewhat longer periods, and the drug would pass less rapidly into the general circulation. It was believed, also, that while specific differences for inhibition of growth of bacteria might be established *in vitro* for different sulfonamide compounds, clinically *sulfathiazole* was equal to the task of holding almost any organism in check. While certain germs do not seem to be sensitive to ordinary blood levels of orally administered sulfonamide compounds, they are clinically much more vulnerable to the high concentrations obtained by local use.

Applied to the mucous surfaces, *sulfathiazole* powder does not stop ciliary action; it disappears slowly, and its absorption seems much delayed. Acute rhinitis, pharyngitis, and laryngitis due to infection with the streptococcus and the hemolytic streptococcus yield quickly to the use of finely powdered *sulfathiazole*, blown into the nostrils, pharynx, and larynx in small quantities by a powder blower, which can be turned in any direction. Gargling with a solution containing 0.5 Gm. (7.7 gr.) tablet of *sulfathiazole* in a quarter-cup of hot water will often bring much relief from local swelling and discomfort. The extreme redness and occasional dangerous edema of the throat, with severe pain in swallowing, associated with such conditions

are greatly helped after one or two applications of the powder. Similarly, after operation on the accessory sinuses insufflation of a thin coating of sulfathiazole powder seems to keep down pain and offensive saprophytic odor to a remarkable degree.

Acute suppuration of the middle ear is not suitable for local treatment with sulfathiazole. In cases of the chronic form, with a wide perforation, it is often possible, however, to remove débris from the attic with the middle ear cannula, dry the cavity carefully, and then blow in a minute portion of the powder.

**Sulfonamide Compounds**—Capus,<sup>27</sup> in an exhaustive study of peritonsillitis and peritonsillar abscess, gives special consideration to the therapeutic value of the sulfonamide compounds. The method of treatment which at present meets with the greatest approval is conservative therapy until fluctuation is believed to be present, when incision and drainage of the abscess are performed. Chemotherapy is not used in this method.

Peritonsillitis and peritonsillar abscess are due principally to a mixed infection, rather than to the beta hemolytic streptococcus. The commonest type of mixed infection, in the author's study, was that due to combination of the beta hemolytic streptococcus and *Staph. aureus* alone or with other organisms. Acceptance of the fact that this disease originates from the spread of an infection from the crypts to the peritonsillar tissues in cases of acute follicular tonsillitis gives added strength to this conclusion. **Sulfanilamide** is not as effective as **sulfathiazole** in the treatment of this disease. Sulfanilamide has a beneficial action, since it causes spontaneous regression in some cases and tends to prevent complications. It is not the drug of choice because recurrences are common with its use. Sulfathiazole is far

superior to sulfanilamide because it causes resorption in a greater number of cases and because recurrences are not common. Sulfathiazole has a decided masking action on the symptoms, without necessarily preventing progression to abscess formation, and so enables one to avoid incision and drainage in most cases of abscess formation, or at least to wait for clearcut evidence of fluctuation before carrying out this procedure. **Sulfadiazine** is probably the drug of choice, but further study is needed to confirm this conclusion.

The dreaded complications of peritonsillar abscess are uncommon when therapy with one of the sulfonamide compounds is employed. Conservative treatment supplemented by use of a sulfonamide compound is far safer and more satisfactory than tonsillectomy.

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## RHINOLOGY

**Cancer of the Nose**—The problem of cancer of the nose and its accessory sinuses has long occupied the attention of rhinologists who, like Schall,<sup>28</sup> now believe that the condition is not altogether a hopeless one. A unilateral mass obstructing a nasal cavity is suggestive of cancer, and when doubt exists, repeated x-ray examinations should be the rule. The rationale of **surgery** for malignant disease of the sinuses may be only that of facilitating adequate drainage. Should the growth be of the anaplastic variety, **irradiation**, either external or interstitial, should be the treatment of choice. If no regression is evident after moderate irradiation, particularly in a lesion of the adult or slow-growing type, then **surgery plus irradiation** is indicated. For nasal growths adequate exposure can be obtained through a latent rhinotomy. After removal of the new growth, the cavity is

lined with vaseline gauze, packed with narrow-folded strips of gauze, in which radium in the form of either platinum or steel needles can be embedded.

The surgical approach to tumors of the sinuses should depend upon the point of maximum involvement. The ideal removal of any cancerous growth is through normal tissue. Incisions usually are made with the cutting electric current, and all bleeders are stopped by electrocoagulation. If operation is likely to disseminate the growth, the entire operative cavity should be electrocoagulated. The local insertion of radium will destroy any scattered tumor cells. Protection of the orbit and other structures is essential when radium radiation is employed.

**Common Cold**—The control of common respiratory infections, especially the common cold, is reviewed by Keefer.<sup>29</sup> He points out that the cyclic incidence of colds in the United States shows three seasonal peaks in January and February, April and May, and September and October. While one attack confers increased resistance to infection, the immunity is of short duration. The seriousness of colds depends on seasonal and secondary infection factors. Although climatic factors and temperature changes are of some influence in the production of colds, virus introduced from the outside is more important than climate.

Present methods of immunization against the common cold have proved ineffective. The results obtained from cold vaccines have been disappointing. Furthermore, large doses of all the vitamins have no significant effect on the number or severity of upper respiratory tract infections in young adults on an adequate diet. To reduce the total number of colds in an individual, personal hygienic measures, avoidance of chilling and sudden temperature changes, and avoidance

of exposure to colds or direct contact may be worth while.

**Infectious Mononucleosis**—Saltzman<sup>30</sup> presents his experience with the administration of bismuth in infectious mononucleosis of the "anginose type." A soluble bismuth compound injected intramuscularly is absorbed rapidly. It is largely deposited in the liver and the mucous membrane of the intestinal tract, particularly the mouth. That the pharyngeal lymphatics share in the distribution of the bismuth has been demonstrated by experimental studies. Pharmacologically, bismuth possesses bactericidal and bacteriostatic properties. It has been used successfully in the treatment of acute streptococcic tonsillitis. The favorable influence of bismuth on the inflammatory processes in the pharynx can be compared to the action of this drug on the superficial lesion of the throat in syphilis.

The author believes that the direct cause of the state of illness from which the patient seeks relief is probably the invasion of the pharyngeal lymphatics by pathogenic microorganisms which cause necrotizing lesions. It was found that bismuth therapy brings about clinical recovery, but apparently has an uncertain effect on the activity of the primary causative agent—virus most likely—which probably is responsible for the abnormal blood picture.

**Nasal Deformity**—Nasal deformity in relation to respiratory function is discussed by Becker.<sup>31</sup> The external or outer nose is frequently overlooked as a possible factor interfering with nasal respiration and hygiene. Since plastic surgery of the nose is more popular today than ever before, more interest is focused on the external nasal structure and the rôle it plays in respiration. The redundant nasal tip, the long nose, the twisted tip, the depressed nose, and de-

formed nasal cartilages have been shown to be important factors in proper nasal breathing. These deformities are sufficient to divert air currents, cause collapse of the alae, and depression of the limen vestibule. The nasal muscles play a prominent rôle in maintaining the proper tonus of the alae.

The external deformity does not necessarily have to be marked to interfere with nasal respiration because, as pointed out by Proetz, even minor defects, such as a septal spur, may interfere with the air currents sufficiently to disturb normal nasal hygiene.

Finally, proper correction of these deformities not only corrects nasal function but cosmetically improves the appearance of the nose as well.

**Nasal Obstruction**—There has been a considerable difference of opinion as to the comparative efficiency of *ephedrine* and its synthetic derivatives in the treatment of nasal obstruction. In order to throw some light on the subject, Sternstein<sup>82</sup> studied the quantitative effects of ephedrine, cocaine, and some proprietary synthetic preparations administered in different concentrations and forms on the erectile tissue in the pathologic nose. In order to evaluate the shrinkage efficiency of a given drug, several factors were considered, such as: (1) The physiologic cycle of erectile tissue swellings; (2) the tonicity of vasoconstrictor solution, and (3) the means by which the drug was administered.

The investigation revealed that the shrinkage efficiency of a drug is diminished in proportion to the pathologic degree of erectile tissue swelling. It was found, furthermore, that *ephedrine hydrochloride* in aqueous solutions is more effective than *cocaine hydrochloride*, except when the latter is combined with ephedrine hydrochloride, in the treatment of acute infections of the up-

per respiratory tract, chronic hypertrophic rhinitis, and polypoid conditions with associated fixed tissue changes. Finally, this study showed that synthetic derivatives of ephedrine and its analogues, such as *amphetamine (benzedrine)* and *neosynephrin hydrochloride*, are more effective than the natural ephedrine. Of the two drugs, neosynephrin hydrochloride, 0.25 per cent, appears to be the more efficient vasoconstrictor agent, judged by its comparative action in the nonobstructed nose.

**Nose Drops**—Several articles during the past few years have given discouraging facts on the use of oily "nose drops." It is claimed that in children in particular lipid pneumonia has been an occasional complication. These reports do not, however, speak against the instillation of oily preparations directly into the paranasal sinuses. Coincidental observations have been made on the favorable therapeutic effects of iodized oil when this oil was employed as a radioopaque for roentgenographic purposes. Now, Littell<sup>83</sup> describes the treatment of chronic sinusitis with 27 per cent iodized and 7.5 per cent *chlorinated peanut oil* in 50 per cent combination with *oil of sesame*. This combination of oils is more readily injected because of its lower viscosity. Only in a few instances have there been unpleasant vasomotor symptoms in the nose after its use. In these patients there was, as there occasionally is, a sensitivity to iodine. The author believes that there is an absorption of iodine by the tissues, even though, as Proetz remarked, the solution employed is chemically inert, in fixed combination, and the iodine is not given off separately. The most spectacular results have been noted in cases in which a partial allergic or vasomotor background may be suspected. Experience has also been favorable in cases of the subacute

or chronic condition. The acute disturbances do quite as well with lavage, or lavage followed by the injection of a 5 per cent solution of sulfathiazole. But lavage is less dramatic with low grade disturbances, and it is here the injection of oil occasionally seems to have a place.

### Rhinitis

**Allergic Rhinitis**—The symptomatic and empiric treatment of the allergic nose in cases in which rhinitis was refractory to treatment was studied by King and King.<sup>34</sup> They emphasize that rhinologists must keep in mind the general physical condition of the patient as an important aspect when nasal symptoms are being evaluated. Shrinking solutions and vapor are overused and prove harmful to some patients. In many instances, discontinuance of these remedies has in itself cleared up the symptoms. The following recommendations are made by the authors: (1) Determine the skin reactions as soon as possible. (2) Control the environment. (3) Try diets strictly free from milk and wheat over extended periods. If there is no response, bacterial allergy must be considered. Cultures of the nose and sinuses can be made, and the administration of *stock vaccines* should be started. A trial should be made of the various empiric remedies, such as *histaminase*, *thyroid*, and the *estrogens*. *Chemotherapy* should be given in selected cases. A careful record should be kept of the procedures used and the length of trial of each. Good results in the vast majority of cases will come only through careful, painstaking effort with each patient.

**Atrophic Rhinitis**—Although numerous articles have appeared on the use of *estrogen therapy* in atrophic rhinitis, the rationale of this method of management has not been definitely estab-

lished. Ruskin<sup>35</sup> investigated the problem and concluded that the differential diagnosis of primary atrophic rhinitis (ozena) and secondary atrophic rhinitis is essential in the proper use of estrogenic therapy. From experimental studies it was apparent that a hormone mechanism related to the pituitary gland and possessing estrogenic properties is a normal constituent of the nasal mucosa. The observation also allows a degree of speculation that, since the pituitary gland is concerned with blood vessel tone, pronounced thickening of the blood vessel walls shown in the pathologic picture of primary atrophic rhinitis is the end result of tonic overaction of the vasoconstrictor fibers, caused perhaps by a deficiency of the pharyngeal pituitary. The occurrence of nasal and nasopharyngeal congestion during pregnancy also suggests the possibility that the pharyngeal pituitary exercises an active vasodilator influence on the nasal mucosa. The relationship of the nasopharynx to primary atrophic rhinitis may also be seen in the constant occurrence of crusting, pallor and, in some instances, scarring in the region of the pharyngeal pituitary.

If estrogenic substance is used in cases of primary atrophic rhinitis (ozena), in which the blood vessel walls are thickened and constricted, the vasodilator influence incident to estrogenic stimulation has a definite value and provides desirable effects.

Three types of medication were tried: (1) A nasal spray of estrogen in oil alone; (2) a nasal spray of estrogen in oil combined with parenteral injections, and (3) oral administration of estrogen tablets. The combined nasal spray and parenteral injection of estrogen in oil was the most effective.

The first essential in therapy is the differential diagnosis of primary atrophic

rhinitis (ozena) of vascular origin and secondary atrophic rhinitis resulting from a severe nasal infection. The primary atrophic rhinitis is apparently related to involvement of the pharyngeal pituitary and the pituitary gland, and is amenable to treatment with estrogenic substances. Extracts of the nasopharynx also possess estrogenic properties. Treatment of secondary atrophic rhinitis should be studied from the point of view of determining the infective agent and using specific remedies when possible.

### Sulfonamide Therapy

**Effect on Mucous Membrane—**Since the local application of the sulfonamides has found a place in surgical therapy, rhinologists have conducted experiments to determine whether these compounds are of any value in nasal and sinus conditions. Clinically, there has been and still is considerable optimism concerning the favorable local effect of *sulfathiazole* and the other sulfa preparations. The problem seems to resolve itself, however, on the effect of these on the mucous membrane, which in the opinion of Hunnicutt,<sup>36</sup> has not been clearly defined. To clarify the situation they conducted a study to determine the effect of sulfathiazole in different percentages instilled in noses of mice. Inbred Swiss mice were used, as developed by the Rockefeller Foundation. The mice were treated with 0.5, 1 and 5 per cent solutions of sodium sulfathiazole. Since the 5 per cent solution has been recommended in literature, more extensive experiments were carried on with it. The author found that sodium sulfathiazole in a 5 per cent solution is an irritant to the nasal mucous membrane in the mouse and produces a purulent exudate and inflammation in the first three or four days of its use. Thus, up through two weeks of its use, the inflammatory reaction sub-

sides and almost no irritating effect is seen, as noted by lack of epithelial change or purulent exudate. The olfactory mucous membrane is not permanently injured. It can thus be concluded that in the mouse there are no permanent ill effects from the use of a 5 per cent solution of sodium sulfathiazole.

**Sulfallantoin—**The use of a sulfonamide compound in nasal therapy is discussed by Joseph S. Stovin,<sup>37</sup> who summarizes his studies as thus:

1. *Sulfallantoin* is a combination of sulfanilamide and allantoin which lends itself to use in intranasal therapy.

2. The aqueous solution used was hypertonic and acid (with a pH of 5.4), thus fulfilling the essentials for a good nasal spray.

3. The sulfanilamide radical is bacteriostatic.

4. The allantoin radical is an effective stimulant to healing. It also has the desirable property of neutralizing certain sulfonamide inhibitors, whose presence would otherwise interfere with the action of the sulfanilamide.

5. Sulfallantoin is also efficacious when introduced directly into the diseased sinuses in its original powder form.

6. A series of ten cases is described in detail. These consist of acute, subacute, and chronic stages of disease and demonstrate the various methods in which the preparation can be used. As a result of this study the author concludes:

A valuable therapeutic agent, sulfallantoin, has been added to the armamentarium of the otolaryngologist. It has conclusively proven its worth in all types of sinusitis of infectious origin. It is of particular value in subacute and chronic cases where it is desirable not only to eradicate the infection, but also to stimulate the growth of a healthy lining membrane. Because of the ease with which

it can be introduced into the nasal cavity and sinuses, it should be given a trial before more radical therapeutic procedures are undertaken.

**Sulfathiazole** — Sulman<sup>38</sup> conducted a study to determine the therapeutic value of *paredrine hydrobromide-sulfathiazole suspension* in infections of the upper respiratory tract. Many investigations have shown that *sulfathiazole* (2-(para aminobenzene sulfonamid)-thiazole) is the most effective of the sulfonamide compounds so far studied against the majority of the bacteria present in the nasal cavity. Sulfathiazole administered intravenously or by mouth in sufficient quantities to be effective against masses of bacteria such as can collect in the sinuses and eustachian tubes may have toxic effects. It has long been thought that the ideal medication of the nose would be one which would both reduce nasal congestion and destroy pathogenic organisms without injury to the cilia. The suspension of sulfathiazole in an aqueous solution of paredrine hydrobromide has none of the caustic effects reported for sodium sulfathiazole.

Sulman treated 75 patients with rhinitis and sinusitis with this suspension over a period of eight months. It proved successful in reducing nasal congestion and in decreasing and/or eliminating discharge, without evident injury to the cilia. There have been no untoward effects of any kind. Its use has shortened the course of infection for many patients and averted sequelae to colds. The amount employed is so small that it can be used repeatedly without systemic reactions from either the sulfathiazole or the paredrine hydrobromide component.

The nares are first shrunk with a 1 to 3 per cent solution of *paredrine hydrobromide*, and then suction is applied. Then either of the nares are packed with the suspension or drops are instilled.

For use in the displacement method by Proetz the paredrine-sulfathiazole preparation is diluted 1 to 5 with sterile physiologic solution of sodium chloride. The displacement method is used twice a week as long as necessary. In home treatment 2 to 5 dilution of the suspension is instilled in each nostril two to four times daily until cure is obtained.

**Upper Respiratory Infections** — Janeway<sup>39</sup> reviews the problem of treatment of upper respiratory infections in children with special reference to the use of sulfonamides. Should one of these preparations be considered indicated, it should be given a two- or three-day trial to ascertain whether or not the therapy is of value in the given case. Toxic reactions and sensitization to the drug must be guarded against, the latter in particular, since its use is often precluded because of severe reactions in serious infections when the drug is urgently needed.

In indicated cases the *sulfonamides* should be given intensively and early, but as soon as the infection is controlled the dose should be lowered. The possibility of kidney involvement must be entertained during therapy. With administration of the newer sulfa drugs hemolytic reactions are rare. Of the newer preparations of the sulfonamides, *sulfadiazine* is the most satisfactory. Its sodium salt may be given parenterally. *Sulfathiazole* may be used in place of and in the same doses as sulfadiazine, but it is excreted more rapidly and therefore the maintenance of adequate concentration in the child by its parenteral use without development of renal complications is more difficult. As soon as the patient is able to take the drug by mouth, administration by injection methods should be discontinued. The dose of the drug given parenterally is the same as that given orally. Since vomiting oc-



curs more often in sick children than in adults, parenteral administration of the sulfonamides is used quite frequently in children.

As for nose drops, the author favors a water base. He deprecates the use of the sulfonamides for nasal medication because the incidence of sensitivity through the nasal mucosa is high, especially for sulfathiazole. However, sensitization to one sulfonamide does not necessarily imply a similar reaction to all other sulfonamides.

In virus respiratory infections, according to the author, one is no more justified in using the sulfonamides by mouth in every cold than in giving digitalis every time the heart rate increases over 100.

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## CLINICAL PATHOLOGY

FRANK W. KONZELMANN, M.D.

### The Cytology of the Polymorphonuclear Leukocyte in Toxic Conditions

It has been properly pointed out by many pathologists that the degree of infection or toxemia is not always accu-

rately reflected by the Schilling count (or any similar estimation of the less mature leukocytes) and correspondingly noninfectious conditions such as simple hemorrhage may result in a leukocytosis with a "shift to the left." Ponder and Ponder<sup>1</sup> report that a simple study may

be made of the changes occurring in the structure of leukocytes which does more accurately reveal the severity of a toxic state and when this is combined with some one of the methods which classify leukocytes according to age, a more accurate diagnosis is possible from a hematological standpoint.

These authors point to the necessity of a precise technic. Glass slides are well washed in a soap powder solution (Gold Dust), rinsed thoroughly in hot running water, dipped in 95 per cent alcohol, and wiped dry with a clean towel. They advise against the use of acid alcohol or acid cleaning solutions, for these affect the staining qualities of the film. Films are prepared from fresh blood or heparinized blood, never from oxalated blood. They are fixed in pure, acetone-free methyl alcohol for five minutes and then air dried. Giemsa stain is employed in a dilution of 1 to 10 in freshly distilled water. This dilution is prepared immediately before staining. Films are placed flat upon a rack, flooded with diluted stain. The staining period is exactly 30 minutes. The film is then washed in running distilled water 15 seconds, flooded with distilled water 30 seconds, drained, and allowed to dry in air. These authors recommend the count of Cooke and Ponder (1928), wherein the neutrophils are recorded according to the number of lobes of each nucleus. The number of one lobed nuclei is multiplied by one, the number with two lobes by two, etc. One hundred polymorphonuclears are so counted and recorded. The sum of the products obtained above is divided by 100 and the factor resulting therefrom is called the polynuclear mean. The normal ranges from 2.3 to 2.7. Means less than 2.3 constitute "left-handed deflections." One may perform with equal success the filament-nonfilament count. During this nuclear count

one observes the staining properties of the neutrophils and mentally notes the following changes:

1. Cytoplasmic granules are large, separated, and deeply stained. (Toxic granulation.)

2. The cell outline is irregular and hazy instead of circular and sharp. (Ameboid.)

3. Vacuoles in the cytoplasm.

4. Pyknosis of nuclei. Nucleus as a whole or in part shrunken and heavily stained.

Each factor may then be graded from 0 to 4 according to the impression formed during the nuclear count. The values assigned for factors 1 and 4 and half the sum of 2 and 3 (since these are expressions of protoplasmic change) are added to obtain a "grade" of toxicity. Values of 0 to 12 are obtainable. In a series of cases studied by these authors, in those showing no clinical signs of toxicity, such as cases of carcinoma or gastric ulcer, the total count was frequently found above 10,000, the percentage of neutrophils as high as 82 per cent, and the polynuclear mean 1.36 (indicating a rather marked left shift), and a grade of 2 or less than 2 was obtained. (One case of carcinoma of the hepatic flexure was graded 3). In another series showing marked clinical evidence of toxemia from infection or toxic states, the total count was below 10,000 almost as often as it was above. The percentage of neutrophils was not constantly high and while there was a relatively frequent shift to the left, it was not constant even in infectious states, yet the grade of toxicity was constantly above 7. The authors have also demonstrated by table that improvement in a case is evidenced by a fall in grading while a poor prognosis is indicated by a rising grade.

### Effect of Posture on Hemoconcentration

Quantitative changes in the composition and cellular elements of the blood over relatively short periods often have great diagnostic significance. Even the lesser changes not going far beyond the normal range may be of importance. However, we often fail to realize the effect of a change in habit and in posture brought about as the patient becomes a subject for study. Not the least of these is the effect caused by the change from the erect to the recumbent position. Perera and Berliner,<sup>2</sup> while investigating paroxysmal dyspnea, have demonstrated the effect of change in posture on hemoconcentration. These authors performed red cell counts, red cell diameter, hematocrit, serum protein, vital capacity, and venous pressure determinations on ten normal individuals at 4 P. M. and 11 P. M., employing venous blood. The night data were obtained after at least one hour of rest in bed or sleep. Red cell counts fell from 180,000 to 370,000 in eight of the ten cases. There was no change in mean corpuscular volume or cell diameter. Vital capacity fell 100 to 400 cc. Venous pressure rose 5 to 20 mm. In cases of paroxysmal dyspnea a rapid rise occurred in serum protein. Venous pressure rose higher and vital capacities fell lower in those suffering an attack after assuming the recumbent position than in those who did not. Perera and Berliner quote Thompson who, in studies on plasma volume, showed a drop of 11 per cent in subjects changing from a recumbent to an erect posture. In the opinion of these authors, one may attribute these physiological variations to some pathologic state such as malnutrition, shock, or operative protein loss unless the effect of postural change is kept in mind. They believe further that the slightly greater degree

of venous and pulmonary congestion occurring in the recumbent state, as measured by the vital capacity and venous pressure, is in accord with the concept of a larger and more dilute blood volume. It is the increased fluid volume that causes a strain on an already overburdened left ventricle. They believe the interpretation of these changes must be guarded.

Yeomans, Porter, and Swank<sup>3</sup> have made somewhat corresponding studies on dogs subject to rapid venous infusion. Animals developed congestion in the peripheral, pulmonary, and portal venous systems evidenced by a rising venous pressure, swelling of the liver, spleen, and in some cases pulmonary edema. Plasma volume increased and serum proteins fell. There was an increase in heart size and a change in heart rate and rhythm.

### Urea Rise in Hypochloremia

The rise of blood urea in hypochloremic states is well recognized. By some at least it has been considered an obvious result of loss of serum electrolyte, perhaps in an effort on the part of the body to maintain osmotic equilibrium. Kirsner, Palmer, and Knowlton<sup>4</sup> produced gradual chloride deprivation in two adults with pyloric obstruction secondary to duodenal ulcer by Wangenstein aspiration of gastric contents. Their patients were given no fluid or food by mouth but 3000 to 4500 cc. of glucose in distilled water were administered intravenously each day. Chlorides fell to 53.8 mM/L in one and 58.9 mM/L in the other. The maximum blood urea nitrogen in the first was 30 mg. per cent and in the second 23.1 mg. per cent. The blood sodium and total base fell, patients lost weight, and the hematocrit and plasma proteins rose. Though there was adequate fluid administered, dehy-

dration occurred because fluid could not be retained in the body with such a marked depletion of electrolyte. Gamble has also shown that an abrupt depletion of chloride is associated with an equally abrupt loss of sodium and body water. The loss of fluid decreases the circulating volume which, by reducing the venous return to the heart, lowers cardiac output and leads to peripheral circulatory failure. Blood flow through the kidney and effective glomerular filtration pressure are consequently lowered. The nitrogen retention and decreasing renal function evidently represent a decreased renal circulation rather than intrinsic renal disease. These authors attribute the absence of azotemia in these two cases to two factors:

1. The gradual depletion of chloride allowed the patient to make fairly satisfactory adjustment to severe electrolyte loss.
2. Daily administration of large amounts of water tended to wash out the urea nitrogen and maintain adequate blood flow through the kidney.

### Studies of Pancreatic Function

**Blood Amylase**—Polowe<sup>5</sup> has reviewed the subject of blood amylase activity and proposes a short easy method for its determination. According to Polowe the exact nature of amylase and its source are not known. It is apparently present in the albumin fraction of the plasma of man, rabbit, sheep, and dog, but only in the globulin fraction of the plasma of the horse. Polowe, quoting Blom *et al.*, distinguishes two forms—alpha and beta amylase as determined by their liquefying and saccharifying powers and their ability to affect the interaction of starch and iodine. Numerous organs have been excluded as the source of amylase, even removal of the pancreas which, although

it is followed by a fall in amylase activity of the blood, the level rises to normal shortly. Polowe sums up the present day knowledge of alteration of blood amylase activity as follows:

**Increased Activity**—Pancreatic disease, pneumonia about the time of crisis (two out of three cases), perforation of peptic ulcer in or near the pancreas, high intestinal obstruction, salivary duct occlusion, suppuration or mumps, impairment of renal function, adrenal cortical insufficiency in the dog.

**Decreased Activity** — Obstructive jaundice, pneumonia and other infections, primary malignancy of the liver and bile ducts, acute cholecystitis, heart disease, impairment of renal function, diabetes mellitus, toxemia of pregnancy, drug poisoning, burns with liver damage and loss of serum protein, hyperthyroidism in the presence of impaired liver function, and shock due to hemorrhage.

For the determination of amylase activity in suspected pancreatic disease, the test must be performed within 48 to 72 hours of the onset of the disease. Polowe suggests a simple method for the rapid determination of amylase activity. He adds 0.5 cc. of plasma or serum to 4.5 cc. of a 3 per cent soluble starch solution. This he incubates for 30 minutes at 37.5° C. Then he adds 0.5 cc. of this plasma or serum starch solution to 4.5 cc. of Benedict's qualitative copper solution, boils in a water bath for five minutes, and then centrifuges. A normal control is carried along in a similar fashion. The cuprous oxide which forms a ring or button in the bottom of the tube is compared with the unknown and the latter is reported normal, decreased, or increased in accordance with the size of the button as compared with the normal control.

Siegel and Krautman,<sup>6</sup> using Somogyi's method for the serum and that

of Dozzi for the urine, found the serum diastase decreased and the urine diastase increased in the acute alcoholic state of the chronic alcoholic individual.

**Blood Lipidase**—Roe and Goldstein,<sup>7</sup> experimenting on cats, attempted to investigate both amylase and lipidase activity following injury to the liver or pancreas. Animals were divided into four groups as follows: Group I received eserine and mecholyl; Group II pancreatic duct ligation with mecholyl stimulation; Group III pancreatectomy, and Group IV chloroform poisoning for the purpose of damaging the liver.

Stimulation with mecholyl in the presence of eserine with and without ligation of the pancreatic duct resulted in an increase in the lipoidolytic and amylolytic activity of the blood. Pancreatectomy resulted in a postoperative decrease in serum amylase and lipidase, with mixed return trends toward normal levels demonstrating that amylolytic and lipoidolytic enzymes of the blood have, in addition to a pancreatic source, an extrapancreatic source. Chloroform poisoning caused a decrease in serum amylase.

By varying the substrate in a new method which they have devised, these authors were able to demonstrate a dissociation of effects upon blood lipase in animals poisoned with chloroform.<sup>8</sup> Enzymes capable of splitting triolein and olive oil were slightly decreased and the enzyme or enzymes capable of splitting ethyl butyrate, benzyl butyrate, and tributyrin were definitely increased.

#### Estimation of Sulfonamide Level in Serum

Laboratory methods which are simple in technic and yet sufficiently accurate for clinical use are of inestimable value, especially in the small hospital or in the emergency when time and the lack of an experienced laboratory worker may de-

mand either a simple procedure or none at all. La Rosa<sup>9</sup> has devised a test paper for the rapid estimation of the level of sulfonamide in the serum. He dissolves 1 Gm. of p-dimethylaminobenzaldehyde (straw colored material is usable) in 2 cc. of concentrated hydrochloric acid. To this solution he adds 0.8 cc. of syrupy phosphoric acid (Sp. Gr. about 1.7) and water to make 100 cc. Large pieces of absorbent paper, such as is used for making litmus paper, are soaked in the solution and immediately hung up to drain. When superficially dry the paper is stored in the dark in covered glass jars for five to ten days. During this time most of the hydrochloric acid will evaporate. The edges of the paper will usually turn yellow. The yellow edges are trimmed and the paper cut into strips and stored in suitable vials. These strips are almost colorless. Care must be taken in the preparation of the paper, for wherever it touches the skin it will become discolored.

Satisfactory color standards may be made by reproducing the color caused by sera of known concentration with water colors or suitable dyes. Combinations of picric acid and Orange G have been satisfactory. A single color standard is suitable for the estimation of sulfapyridine, sulfathiazole, or sulfadiazine. For sulfanilamide the values read from this standard should be divided by 1.5. The color ranges from a pale violet with normal human serum to a bright yellow with serum containing 15 to 20 mg. sulfadiazine per 100 cc.

This method cannot be employed with fluids containing variable amounts of protein nor with urine. Sulfonamide values for whole blood are not directly transferable to serum; values for the latter are usually higher for the same blood sample.

Other primary aromatic amines including p-aminobenzoic acid as well as free sulfonamides will give a similar color. Urea in pathological concentration yields significant amounts of color. Alterations in protein content of the serum may lead to inaccuracies. It is important to keep the test papers in a cool place away from direct light and moisture.

Estimation of the sulfonamide level is made by spreading evenly the serum to be tested over one end of an impregnated strip by means of a fine dropper, care being taken that unabsorbed fluid does not remain. Within 10 seconds a maximum development of color occurs. The wet strip should be held close to a white background, such as porcelain or white paper, to avoid an alteration in intensity of color being caused by translucency of the wet strip. Comparison of color with that of the standard strips is made immediately. For convenience the author has grouped his colors in intensities corresponding to 0-3, 3-6, 6-9, 9-12, and over 12 mg. He found that with a little practice, readings agreed within plus or minus 1 mg. with those obtained on the same serum by the method of Bratton and Marshall.

### **Cold Agglutinins in Certain Types of Pneumonia**

Autoagglutination is a phenomenon in which an individual's own red blood cells are agglutinated by his own serum. There is an absorbable agglutinin in the serum and a corresponding agglutininogen in his red blood cells. Landsteiner and others have shown that these substances are present in bloods of normal individuals but not in high titer and they are active only at low temperatures, hence the name—cold agglutinins. The reaction is reversible, so that agglutination occurs when cells suspended in serum are

placed in the refrigerator. When the suspension is moved to room temperature the clumps are easily broken up and the cells resuspended. If the serum is pipetted off while still cold after agglutination has occurred, the agglutinin will have been removed and such serum will no longer cause agglutination under the above circumstances. The cells, placed in warm salt solution, will yield the agglutinin, the clumps will disappear, and the salt solution will now possess the power to agglutinate the same cells. This effect may be demonstrated not only upon the cells of the individual but upon other cells of the same type. Weiner<sup>10</sup> states that the effect may be demonstrated upon the blood of all other human beings. The titer of this agglutinin may be greatly increased, so that agglutination may occur at room temperature in pathological conditions, such as some varieties of cirrhosis of the liver, hemolytic icterus, Raynaud's disease, trypanosomiasis, and severe anemias. Paroxysmal hemoglobinuria is the result of corresponding hemolysins which give rise to the Donath Landsteiner reaction. More recently, Peterson, Ham, and Finland,<sup>11</sup> and Horstmann and Tatlock<sup>12</sup> have reported on the incidence of these cold agglutinins in certain cases of atypical pneumonia.

Helwig and Freis report an interesting case of a male aged 38 who suffered what seems to have been an atypical pneumonia. About a month after this illness he noted that his nose, ears, and hands became purple after exposure to cold. This abnormal discoloration could be produced at will and it disappeared after he returned to a warm inside temperature. During an attempt to do a blood count, massive agglutination of the red cells occurred in the hemocytometer pipette. It disappeared when the diluting fluid was warmed. An extraordinarily rapid sedimentation rate was observed

when his blood was chilled and sedimented in the refrigerator, yet the sedimentation rate of warm blood was normal. Other tests like those about to be described demonstrated the presence of cold agglutinins.

**Method**<sup>13</sup> — Dilutions of patient's serum are prepared from 1 to 4 up to 1 to 4096 in 1 cc. volumes. To each dilution 0.1 cc. of a 2 per cent suspension of washed human red cells of Group O are added. The tubes are placed at 0° C. overnight. Immediately after removing from the refrigerator the next morning, the reactions are read and then read again several hours after exposure to room temperature. If agglutination has occurred in the refrigerator, it should have disappeared after exposure to room temperature, if it is the result of the action of cold agglutinins. Readings are recorded 4 plus if there is a tight disk not disrupted by inverting the tube three times. The tendency to break up into smaller clumps is indicated by 3 or 2 plus and barely visible fine clumps as 1 plus. No agglutination is recorded as 0. The latter authors report on a series of 135 control cases which were all negative and 40 cases of atypical pneumonia. Eight of nine cases examined immediately were positive. The remaining 31 cases were tested after storage of the serum and only 19 cases were positive. Storage of the serum apparently results in a loss or diminution of agglutinin. The reason for the loss is not apparent. If, however, the clotted specimen is stored in the cold it is obvious that the agglutinin will be removed by the patient's own red cells (see first paragraph). The test does not become positive until after the eighth day. There is apparently no clear-cut correlation between the titer and the severity of the disease.

### Vital Capacity

Gross<sup>14</sup> has devised a new spirometric procedure for investigating the respiratory function. He adds to the factor of volume, the time of expiration, and the respiratory pressure which can be developed.

The velocity of spirometric respiration is determined by dividing the volume of expired air in cubic centimeters by the time in seconds required for the completion of the expiratory effort. The respiratory pressure is the maximum height to which the column of mercury can be driven by forceful expiration into a manometer. It is expressed in millimeters of mercury.

**Technic**—Gross employs the Barnes dry spirometer with the patient standing. Two measurements are made of the vital capacity according to the commonly employed technic and the result is expressed in cubic centimeters without reference to body surface area, height, weight, or age. After a few minutes of rest the patient slowly inhales as deeply as possible and then exhales as quickly and as forceful as possible into the mouthpiece of the spirometer. The observer, stopwatch in hand, measures the time elapsing between the beginning rise of the spirometer index tube and the instant when it comes to rest. Care must be taken that no air escapes at the sides of the mouthpiece. Two readings are made and the smaller in time value is utilized. For reliable testing, there should be no greater difference than 200 cc. between the recorded vital capacity as first determined and the volume exhaled for the measurement of the time of expiration.

A baumanometer is employed to record the expiratory pressure. The cuff connection is joined to a rubber tube 50 cm. long, like that attached to the spirometer. The patient inhales deeply as before and then exhales into the



manometer, forcefully driving the mercury as high as possible.

There have been no ill effects from this test. A slight headache, fullness in the head, or vertigo which some patients complain of disappear in a few minutes. Normals (healthy persons 15 to 54 years of age) revealed a vital capacity of 5500 to 4000 (average 4600) cubic centimeters. The minimum time required for exhalation was 4.2 to 2.9 (average 3.4) seconds. The calculated velocity was 1660 to 1110 (average 1340) cubic centimeters per second. These subjects developed a pressure of 186 to 180 (average 119) millimeters of mercury.

There is no intimate relation between vital capacity and expiratory pressure. The velocity of spirometric respiration shows a constant correlation with the absolute value of vital capacity.

**Effect of Disease**—Any decrease in vital capacity caused predominantly by cardiac disease is characterized by prolongation of the expiration time and

marked decrease in expiratory pressure. Decrease caused by pulmonary disease is characterized by even more marked prolongation of the expiratory time but the expiratory pressure is altered little.

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## PEDIATRICS

*Edited by* WALDO E. NELSON, M.D.

### ANEMIA IN CHILDREN

CLARE R. RITTERSHOFER, A.M., M.D.

#### Nutritional Anemia

In a study of nutritional anemia in children and women in wartime Britain, MacKay, Wills, *et al.*,<sup>1</sup> state that it is fair to conclude from the evidence available that in many classes of the community there has been a leveling down on hemoglobin levels. This appears to be due to the leveling down of nutrition since the war and the omission of most of the prophylactic treatment previously given to babies. As against this, the poorest section of the community may well show some leveling up, as the result

of the disappearance of unemployment, the introduction of rationing, and the provision of "priorities" for certain groups.

**Iron Deficiency Anemia**—An investigation was carried out in Edinburgh on infants and school children by Davidson<sup>2</sup> to determine the presence of nutritional deficiencies as evidenced by iron deficiency. The advantage of this method is that iron deficiency can be accurately determined by estimation of hemoglobin concentrations. The hemoglobin levels were estimated in 831 infants, pre-school

children, and school children from working-class families in Edinburgh. The results were compared with a similar series examined in Aberdeen in 1935. After three years of war no significant change was found to have occurred in the hemoglobin levels of infants, but a fall was demonstrated in the case of school children.

### **Achlorhydric Hypochromic Microcytic Anemia**

The diagnosis of this disease in a child eight years old was based upon the blood picture, the persistent histamine refractory achlorhydria, the absence of steatorrhea, and the excellent response to large oral doses of *iron* with regression of the splenic enlargement. The achlorhydria persisted when the blood count was normal. The authors, Dacie and Ellman<sup>3</sup> suggest that the iron deficiency is conditioned by achlorhydria. The etiological relationship between lack of acid secretion and the development of anemia is, however, not quite clear.

### **Physiologic Anemia of Infants**

A two-year study in a well baby clinic to determine if the early addition of solid foods had any beneficial effect on the physiologic anemia of infants was concluded by Brokaw, Sedam, and Cassirer.<sup>4</sup> Their results showed that the introduction of cereals, vegetables, and eggs has no marked effect on the hemoglobin level or the red blood count of infants, but their weight, height, and firm muscle tone were benefited on the whole by these dietary additions in the early months of infancy.

### **Hypoplastic Congenital Anemia**

A peculiar case of hypoplastic congenital anemia in a young infant was reported by Reibell.<sup>5</sup> The outstanding feature in this case was an apparent inability of the bone marrow to produce

blood elements, involving not only the erythrocytes and hemoglobin, but also the granulocytes and, to a lesser extent, the thrombocytes. The deficiency of the bone marrow was apparently temporary in nature, as spontaneous blood regeneration began at 21 months of age. The prognosis in this type of case is apparently good if *transfusions* are given frequently enough to tide the child over the period of bone marrow inactivity.

### **Macrocytic Hyperchromic Anemia in an Infant**

Macrocytic hyperchromic anemia in an infant was reported by Fouts and Garber.<sup>6</sup> The mother of this infant had been on a diet deficient in meat during pregnancy and consequently supplied only minimal amounts of antianemic material for the fetus. This anemia usually is observed in previously healthy infants after an infection of the upper respiratory tract followed by a period of vomiting or diarrhea or both. Free hydrochloric acid is nearly always present in the gastric contents, although frequently decreased in amount. Intramuscular administration of 0.25 U.S.P. units of purified *liver extract* was followed by reticulocytosis, rapid rise in the number of red blood cells, and gain in weight. Anemia does not recur after it has once been relieved.

### **Anemia in Adolescents**

Schwartzman<sup>7</sup> used the red blood cell counts and hemoglobin determinations of a large group of male and female adolescents as a check for the use of pallor as a screening index. Of 934 cases, 106 cases of pallor were detected, but of these only 22 had anemia as proven by the blood count. The remaining 84 cases of pallor had blood counts within the normal range. On the other hand, anemia may be present without any detecta-

ble pallor. In his study 84 cases of anemia were detected by the blood studies which would have been missed if pallor had been depended upon for the diagnosis. The author suggests that every physician should at least do a hemoglobin on all cases regardless of appearances.

### Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria

The first report of a case of this disorder (Marchiafava-Michele syndrome) in a child was made by Pierce and Aldrich.<sup>8</sup> The outstanding clinical features of the disease are chronic hemolytic anemia which is resistant to treatment, constant hemoglobinemia, and an associated type of hemoglobinuria which is induced by sleep. Severe erythrocytic destruction occurs whenever the patient sleeps, and is believed to be due to an abnormality of the patient's erythrocytes which makes them unusually susceptible to very slight changes toward the acid side in the pH of the blood plasma. Ham concluded that the intravascular hemolysis occurs particularly during sleep because the pH of the blood plasma is decreased a very slight but significant amount within physiologic limits due to diminished pulmonary ventilation and resultant increased carbon dioxide concentrations. At intervals following severe hemolytic episodes, dark reddish brown or black urine is excreted. Urine which is voided during or immediately following sleep may show large amounts of hemoglobin, while the specimens which are obtained a few minutes or a few hours after the patient has awakened are frequently negative for hemoglobin or may show only a minimal amount.

The anemia may be classified as a normocytic or slightly macrocytic type. Other features are a constant reticulo-

cytosis, moderate leukopenia, and thrombocytopenia. The erythrocytes show normal resistance to hypotonic saline solutions.

Symptoms include pallor, icterus, and recurrent attacks of severe abdominal or lumbar pain which are frequently associated with chills, fever, and general malaise. There is a moderate degree of hepatomegaly and splenomegaly.

*Splenectomy* has been resorted to in many cases but has failed to prove effective in curing the condition and has resulted in several deaths. *General supportive measures*, such as oral administration of *iron*, *accessory food factors*, *a liberal diet*, and the *avoidance of infections* have been found to be most effective in prolonging life and improving the well-being of the patients. The authors point out that because of the infrequent occurrence of hemoglobinuria and the obscurity of other features in some cases of this disease which have been reported, it seems that all cases of hemolytic anemia which have any unusual or atypical features should be carefully studied to rule out this diagnosis. The test for fragility of the erythrocytes in acidified serum is easy to perform and is sufficient to identify or exclude the diagnosis of Marchiafava-Michele syndrome.

### Erythroblastosis Fetalis

**Clinical Significance of the Rh Factor**—The discovery of the Rh factor (Landsteiner and Wiener, 1940) and the demonstration of its importance in various fields of medicine (Wiener and Peters, 1940; Levine, Katzin, and Burnham, 1941) have recently aroused the keenest interest.

The presence of the Rh factor in certain human erythrocytes was first discovered by testing samples with anti-rhesus sera, prepared by injecting the

blood of rhesus monkeys into rabbits. It was found that 85 per cent of human bloods, irrespective of group, were agglutinated, whereas 15 per cent were not. The former are termed "Rh positive" and the latter "Rh negative." Persons whose erythrocytes are Rh negative are capable, under certain circumstances, of forming an antibody which reacts with the Rh antigen. This may occur after transfusions of Rh positive blood or, probably more commonly, when a woman (herself Rh negative) becomes pregnant with a baby whose erythrocytes are Rh positive.

The rôle of isoimmunization in the pathogenesis of erythroblastosis fetalis was more fully considered by Levine, Burnham, Katzin, and Vogel in 1941. From their examinations it was concluded that isoimmunization of an Rh negative mother to the Rh antigen contained in her (Rh positive) fetus with subsequent passage of the immune anti-Rh agglutinin back across the placenta, was the cause of the erythroblastosis in the great majority of cases. In the small remaining group, in which the mother was Rh positive, it was considered that other blood group differences were responsible.

**Etiology**—One of the theories proposed concerning the etiology of erythroblastosis fetalis employs the concept of an antigen-antibody mechanism as underlying the marked blood destruction which characterizes this disease. According to this theory, fetal blood enters the maternal circulation through some break in the placental barrier and stimulates the production of antibodies which diffuse back into the fetus and destroy its erythrocytes. Obviously for these reactions to occur there must be an incompatibility between maternal and fetal blood. In this case the incompatibility is based upon the existence of the Rh anti-

gen in fetal blood which, upon gaining access to the maternal circulation, stimulates the production of its corresponding antibody in a mother not possessing the antigen.

A number of newborn infants, each of whom within the first three days of life developed jaundice in excess of the degree associated with simple physiologic icterus, were studied by Gallagher.<sup>9</sup> In some of these infants the prominent clinical aspects were those of erythroblastosis; in others they were those of icterus gravis or universal edema; while in some they were merely varying degrees of jaundice with or without anemia. The blood of these infants and of their mothers was tested for the Rh antigen and its corresponding antibody. In this group of 20 mothers of icteric babies, 11 were Rh negative and only 9 were Rh positive. In this study the presence or absence of demonstrable antibody in the maternal circulation appears to bear no relationship to the severity of the disease as observed in the infant. It was possible to demonstrate Rh agglutinins in samples of maternal blood, taken within one week after delivery, in only 3 of the 11 Rh negative mothers. Levine has suggested that the antibody may be hidden in tissue depots, that it may have been present earlier in pregnancy, or that the concentration is so low as to preclude detection with the relatively crude technic currently employed.

The authors do not find in their cases the correlation that has been reported between Rh negative mothers and Rh positive offspring. Accordingly, they believe that a laboratory determination of the Rh status of mother and infant is of limited value in the diagnosis of erythroblastosis, employing the term in a broad sense, as suggested by Diamond, Blackfan, and Baty.

Levine<sup>10</sup> states that the concept of isoimmunization is still further strengthened by the demonstration of anti-Rh agglutinins in the blood of mothers of affected infants. The chances of demonstrating anti-Rh agglutinins are greater if the mother's blood is tested soon after the delivery. In more than 50 per cent of the Rh-mothers tested, anti-Rh agglutinins could not be demonstrated even if tests are made shortly after delivery of an erythroblastotic infant. However, it is conceivable that the immune antibodies, after exerting their effect on the fetus in the latter part of the pregnancy, gradually diminish in intensity so that none could be demonstrated at delivery. Furthermore, even those Rh-mothers of erythroblastotic infants are subject to intragroup transfusion accidents, if Rh+ blood is injected. Presumably, the antibodies, which may have disappeared from the serum, are still present in the antibody producing cells of the reticulo-endothelial system. Another factor determining the low incidence of anti-Rh agglutinins at delivery lies in the limitations in the sensitivity of the technic employed.

**Other Blood Factors**—Other blood factors capable of inducing isoimmunization by pregnancy are already known. Of the mothers with erythroblastotic infants 10 per cent have been shown to be Rh+. It is likely that in this small group of 10 per cent Rh+ mothers, finer differences within the Rh complex, as well as several blood factors other than Rh may be responsible for the isoimmunization of the mother. Experimental data tends to confirm the view that the Rh factor is found in red blood cells only.

**Familial Incidence**—The presence of the Rh factor is inherited as a mendelian dominant property and its absence as a recessive. Consequently, there are

two genetic types of Rh positive individuals, homozygous (RhRh) and heterozygous (Rh<sup>+</sup>rh). In a mating of homozygous Rh+ father and an Rh— mother (rhrh), 100 per cent of the offspring are Rh+, so that each pregnancy offers an opportunity for the immunization of the Rh— mother. If the father is heterozygous, then 50 per cent of the children will be Rh— and therefore incapable of immunizing the mother. In both matings one or more pregnancies with an Rh+ fetus may be required to induce a sufficient degree of isoimmunization so that the subsequent pregnancy with an Rh+ fetus will result in fetal erythroblastosis. Accordingly, if any one surviving normal child is Rh—, then the father must be heterozygous, and such couples may be encouraged to attempt further pregnancies. If the surviving children are Rh positive, the outlook is not so hopeful, because it is likely that the father is homozygous.

In the treatment of erythroblastotic infants it is advisable to give the **blood of Rh— donors**. Obviously, the infant's own Rh+ or any other Rh+ blood is subject to the hemolytic process which for one or another reason still continues in the early neonatal period. It is true that the mother's Rh— blood can always be used, provided there is blood group compatibility. However, since the mother's blood may contain anti-Rh agglutinins, this difficulty may be overcome by removing the plasma from the citrated blood and substituting either saline or compatible normal plasma.

**Mechanism of Immunization by Pregnancy**—In theory the process of immunization of the Rh— mother by Rh+ fetal blood should occur 85 times 15 or 13 per cent of all random matings. The incidence of fetal erythroblastosis is given by Javert as 1 : 438 full-term pregnancies. From this it is evident that

effects of isoimmunization by the Rh+ blood factor are more frequent, especially if the serologic Rh tests are applied in some cases of stillbirths and extended to some miscarriages. One factor operating to reduce the incidence of the effects of isoimmunization is the current tendency to small families, but the most important single factor may be attributable to the fact that not all Rh— mothers are capable of producing immune anti-Rh agglutinins.

A study of the blood smears in 24 cases of fetal hydrops and of icterus gravis was made by Reisner<sup>11</sup> to determine to what extent the blood picture in erythroblastosis simulates the picture seen in experimental anemias due to auto-antibodies. From this material it became evident that patients with erythroblastosis exhibited morphologic alterations in the red cells of the same general type as those seen in clinical and experimental autohemolytic anemias. In 23 cases the Price-Jones curves were biphasic with macrocytic peaks and in one case there was marked microcytosis. Hitherto one of the explanations of the macrocytes present in these bloods was that they were reticulocytes and immature cells which are called forth in response to destruction of blood. However, it appears that the degree of reticulocytosis is not as high as one usually encounters in other hemolytic anemias with a comparable degree of blood destruction, and the possibility of marrow inhibition must be considered. In the presence of macrocytosis the cause of inhibition might theoretically be a lack of the erythrocyte maturation factor stored in the liver. In six cases studied by Reisner in

which differential counts were made on the nucleated red cells, megaloblasts were observed in all of them. Opinion in this country and in Europe inclines to the view that megaloblasts represent an abnormal type of erythropoiesis which occurs in the absence of the hepatic erythrocyte maturation factor. The presence of megaloblasts in these smears may similarly point to hepatic insufficiency as the major contributory cause of the macrocytosis in the cases with high macrocytic peaks. This is not unexpected in view of the many other evidences of hepatic damage in erythroblastosis fetalis.

The author warns against expecting too much from *liver therapy* in patients with erythroblastosis. It must be remembered that the blood destruction going on simultaneously with impaired regeneration in erythroblastosis militates against successful liver therapy. However, the author suggests injections of liver extract as an adjuvant to *transfusion therapy*, particularly during the recovery phase in patients with this disease.

**Skeletal Changes** — Changes in the skeletal systems of five infants with erythroblastosis fetalis were described by Follis.<sup>12</sup> The most striking alteration was a marked increase in density of the bones, seen both in microscopic sections and in x-rays taken postmortem. This change consisted of an increase in the number and thickness of the trabeculae, due apparently to a lack of destruction of the calcified cartilaginous matrix substance which was then covered with a thick layer of bone. The change common to all the cases studied is the increased density of the shafts.

## DIABETES MELLITUS IN CHILDREN

WALDO E. NELSON, M.D.

**Diet**—The observations of R. L. Jackson and J. Kenefick<sup>13</sup> confirm earlier observations that there is a wide range within which the dietary allowance of children with well controlled diabetes mellitus may be varied without losing "tolerance" as measured by the amount of insulin required. Four children with stabilized diabetes mellitus who were emotionally stable and free from infection maintained approximately normal blood sugar values with a constant insulin dosage and constant amount of physical activity while receiving adequate isocaloric diets, regardless of the fatty acid:dextrose ratio of the diet. They conclude that these children with diabetes mellitus whose disease was treated early and was well stabilized had a capacity for utilizing food comparable to that of normal persons. Emphasis should be placed on diets which are nutritionally complete ones and which are similar to the average diet. If these criteria are satisfied, special attention need not be given the fatty acid:dextrose ratio of the individual meals, and probably not of the entire diet.

**Prognosis**—Additional data on the long term growth of diabetic children has been supplied by A. E. Fischer, H. S. Mackler, and H. H. Marks.<sup>14</sup> There is no agreement concerning the average height of children at the onset of diabetes nor of the rate of growth following the development of the disease. The data from Joslin's series would indicate that diabetic children are tall for their age at the onset of the disease and that their subsequent rate of growth is below the average of nondiabetic chil-

dren. The data of Fischer and his co-workers tends to agree with that of Joslin. Others, as for example, Boyd, have found that diabetic children were not above average height at the onset of the disease and that they did not show any constant trend in height at any time before or after onset. It is pointed out that these differences tend to emphasize the many variables which may affect the growth pattern of diabetic children, such as hereditary, geographic, nutritional, morbid, psychosomatic, and socio-economic factors. Some or all of these conditions tend to affect the child at the onset of his diabetes and his subsequent growth; the degree to which they are active must of necessity affect the pattern of the individual child.

In this study 20 of 23 boys and 16 of 19 girls for whom there were measurements within a short time of the onset of their diabetes were either tall or average in height. The significance of these figures appears to be enhanced by the fact that a majority of the patients were offsprings of immigrant Jews from eastern Europe, while others were of Italian or Puerto Rican parentage, all of whom racially tend to be of short stature. All were from the low income group. The average rate of growth of both boys and girls in this series subsequently fell below normal. There was a tendency for the boys to be underweight and for the girls to be overweight during the years of puberty. Since the caloric intake was estimated to be similar, the greater physical activity in boys was thought to explain the differences in weights in the sexes.



## DIGESTIVE SYSTEM

NINA A. ANDERSON, M.D.

## Peptic Ulcer

A. B. Newman<sup>15</sup> has recommended roentgen examination of the gastrointestinal tract whenever abdominal symptoms are obscure. The diagnosis of peptic ulcer is basically a roentgenographic one. If the duodenal bulb shows irritability and irregularity without actual formation of a crater and these changes persist after the administration of *atropine*, it is his opinion that the diagnosis of ulcer is presumptive and such patients should receive routine therapy. He also stated that the cure of the greater part of cases can be obtained from *alkali therapy*, but that *subtotal gastrectomy* may be necessary for chronic or intractable bleeding.

## Small Intestines

In a study of presumably normal infants and children H. Zwerling and W. E. Nelson<sup>16</sup> found wide variations in the roentgenologic pattern of the small intestine. Some of these changes were of the order which have been reported in certain deficiency states. From their data it would appear that the roentgenologic appearance of the small intestine cannot be considered as a reliable criterion for such diagnoses.

## Typhoid and Paratyphoid Fevers

M. Greenberg<sup>17</sup> has reported that positive Widal tests may be obtained in instances of infection with members of the *Salmonella* group other than paratyphoid A and B. For this reason he emphasizes that recovery of typhoid or paratyphoid bacillus from the blood or the stool is essential for a definite diagnosis.

S. Bornstein and H. Schwarz<sup>18</sup> recommend the use of agglutination tests

with a variety of *Salmonella* antigens as well as repeated stool and blood cultures in instances of doubtful infections of more than a week's duration.

## Infant Diarrhea

To control the reduced activity of the duodenal enzymes and secretions which results in diarrhea in infants, W. C. Davison<sup>19</sup> administered orally commercial *enzymic preparations*, containing 7500-350,000 amylase units and 550-72,000 trypsin units per gram, in doses of 0.3-1.5 Gm. (5-24 gr.) *holadin*, 0.4 Gm. (7 gr.) *taka-diastase*, 2.5 to 5.0 Gm. (40 to 80 gr.) *pancreatin*, or 2.5 Gm. (40 gr.) *desiccated pancreas* six to eight times daily for 3 to 18 days to 23 infants, ranging from 5 to 36 months of age, of whom 18 had acute diarrhea, four chronic diarrhea, and one pyloric stenosis. Beneficial results were obtained in 16 instances as evidenced by gain of weight, improvement of appetite, and fewer and better formed stools.

*Sulfadiazine* and *sulfapyrazine* seemed equally effective in a group of patients with infantile diarrhea treated by R. B. Tudor.<sup>20</sup> There were no toxic reactions. Fifteen patients received sulfadiazine and 22 sulfapyrazine from the day of admission to the hospital until all symptoms and signs of infection had ceased, in dosage of 0.1 Gm. (1½ gr.) per Kg. of body weight per 24 hours. There were 14 cases of bacillary dysentery of which six received sulfadiazine and eight sulfapyrazine, with a cure attained in an average of 4.1 days and 3.6 days, respectively. Of the 23 cases of parenteral diarrhea, nine received sulfadiazine and 14 sulfapyrazine, and there was a clinical cure in 3.7 days and 3.1 days, respectively.

### Dysentery

E. Rubens, M. Kaplan, M. P. Borovsky, and M. L. Blatt<sup>21</sup> demonstrated definite value of *sulfathiazole* (0.1 Gm. [ $1\frac{1}{2}$  gr.] per lb. of body weight per day in divided doses every four hours) in the treatment of those patients whose stool cultures were positive for dysentery or *Salmonella* organisms. The average duration of disease after the treatment was started was 2.9 days for those patients whose stool cultures were positive, 4.7 days for those whose stool cultures were negative, and 8.8 days for those who received no chemotherapy.

It is possible that the bacteriostatic effect of sulfathiazole may mask the presence of dysentery organisms. H. Yannet, A. Leibovitz, and J. V. Deutsch<sup>22</sup> confirm the beneficial effects of *sulfathiazole* in the clinical treatment of dysentery but not for its epidemiologic control. Culture material was obtained by inserting the cot-covered finger moistened with tap water into the rectum and rubbing the finger on the mucosa. The finger cot is cleansed by a cotton applicator that had been tubed and sterilized in 3 cc. of 30 per cent glycerin-saline solution (glycerin 300 cc., distilled water 700 cc., sodium chloride 6 Gm., dipotassium hydrogen phosphate 3.1 Gm., and potassium dihydrogen phosphate 1 Gm.). The applicator is then replaced in the glycerin-saline solution. In the laboratory the exposed swab, after thorough agitation in the glycerin-saline solution, is removed and used to place a drop of suspension on a MacConkey's plate (Difco), whose surface is streaked with a wire spreader. After incubation at 37° C. for 24 hours, suspicious colonies are fished out, inoculated into Kligler's iron agar (Difco) tubes and again incubated. Tubes showing acid butts, alkaline slants, and no gas nor hydrogen sulfide formation are then subjected to

further study by appropriate biochemical and serologic procedures.

In an epidemic of Sonne dysentery, the onset was sudden with abdominal cramps, diarrhea, and in most instances vomiting. The fever ranged from 100° to 105° F. All cases were relatively mild; there were no fatalities. Of 44 cases among the 166 inhabitants of three infected cottages at the training school, 17 received *routine treatment* and 27 received such treatment plus *sulfathiazole*. In the younger age group, six to ten years of age, 43 per cent of them were ill and 13 per cent were carriers of Sonne dysentery. In the oldest age group, over 16 years of age, only 6 per cent of them were ill and 2 per cent were carriers. The dose of sulfathiazole was 3 to 6 Gm. (45-90 gr.) per day, depending on the weight, in four to six doses per day for an average of four days. No toxic reactions occurred.

Among the controls, negative stool cultures were obtained  $19.7 \pm 3.7$  days after the onset. Among those treated with sulfathiazole, negative stool cultures were obtained  $33.9 \pm 4.4$  days from cessation of therapy. In 20 of 27 patients there was a return of positive culture within three weeks after treatment was stopped. There were no relapses among the control group.

Six carriers were treated with 3 Gm. (45 gr.) of *sulfaguanidine* per day for seven days. One case developed diarrhea five days after and responded to treatment with *sulfathiazole* though the rectal culture was positive for two months.

G. M. Lyon<sup>23</sup> reported that *sulfaguanidine* was effective in the treatment of acute bacillary dysentery when the therapy was instituted in the early course of the disease, within five days of onset of fever or of diarrhea. The dose administered was 0.05 Gm. ( $\frac{1}{2}$  gr.) per

Kg. of body weight every four to six hours, up to five days. When the treatment was not instituted until six to ten days after onset, almost as good results were obtained by the management of *diet*, of *fluid intake*, and of other properly indicated therapeutic measures. No "postdysentery" intestinal indigestion was noted among the treated cases. There were no toxic manifestations.

P. F. Lucchesi and N. Gildersleeve<sup>24</sup> used *sulfanylguanidine* in the prophylaxis of an outbreak of dysentery in a group of 118 hospital ward patients. The dose of 0.05 Gm. ( $\frac{1}{2}$  gr.) per Kg. of body weight every four hours for the first day and then every eight hours for two days was given to each of 45 patients in intimate contact with children who developed clinical dysentery, and none contracted the disease. Among 48 children less intimately exposed who received no prophylaxis, four developed dysentery. The clinical cases of dysentery were controlled in four to six days with sulfanylguanidine therapy. The dosage was 0.1 Gm. ( $1\frac{1}{2}$  gr.) per Kg. initially, then 0.05 Gm. ( $\frac{1}{2}$  gr.) per Kg. every four hours until the stools were less than five, and then 0.05 Gm. ( $\frac{1}{2}$  gr.) per Kg. until the stools were formed. Untoward results were negligible.

### Celiac Syndrome

Among 19 cases of cystic fibrosis of the pancreas C. E. Snelling and I. H. Erb<sup>25</sup> reported that *Staphylococcus aureus* was recovered from the lung in all but one instance, in which no culture was obtained. The age range of this series was 2 to 21 months; 11 of the patients were female. Though the series was a survey for 20 years, 11 of the 19 cases had occurred in the past  $1\frac{1}{2}$  years. The symptoms were divided into those which were nutritional, such as failure to gain or loss of weight, vomiting, loose

and frequent stools, colic and abdominal distention, and those which were respiratory, such as cough, wheezing, rapid breathing, and cyanosis. All of them had malnutrition, abdominal distention, and hepatic enlargement. The respiratory disturbances included bronchitis, collapse or consolidation of the lung, bronchopneumonia, and bronchiectasis. Roentgenograms showed increased linear markings, fibrosis, pulmonary collapse, shift of the mediastinum, and consolidation. In spite of chemotherapy and bronchoscopic aspiration, death occurred. Autopsy revealed fibrosis and cystic changes of the pancreas. In the lung there were plugging of numerous bronchi and bronchioles with thick, tenacious, green or yellowish, purulent exudate, bronchiectasis, multiple abscesses, and recent lobular pneumonia. There was fat in the liver cells.

L. J. Flax, M. Barnes, and J. L. Reichert<sup>26</sup> suggested the use of *prostitigmine* as a means of increasing the gastrointestinal tone and motility in cases in which vitamin A absorption was defective. Their schedule of treatment included a *high caloric, high protein, moderately low fat, low starch diet; pancreatic granules*, 1-5 Gm. (15-75 gr.) daily; *vitamin A*, 50,000 I. U. daily in divided doses; adequate amounts of *vitamins B, C, and D*; and *prostitigmine bromide* 3.75-7.5 mg. t.i.d. They reported that the vitamin A absorption curve was normal within 5 months in their cases; there were no toxic symptoms or ill effects from the treatment. There was a diminution in the cough, and lessened peribronchial infiltration of the lungs. Cholesterol levels rose from 114 to 169 mg./100 cc. of blood, suggesting an increase in lipid absorption as well.

C. F. McKhann, S. Spector, and E. R. Meserve<sup>27</sup> have suggested an association

of gastrointestinal allergy with some cases of celiac syndrome. Absorption from the gastrointestinal tract of a fat soluble substance, vitamin A, may be impaired in allergic conditions in which gastrointestinal symptomatology is minimal, which suggested that degrees of impairment of absorption may occur on an allergic basis and that gastrointestinal allergy may bear a causal relationship to the celiac syndrome.

C. D. May, J. F. McCreary, and K. D. Blackfan<sup>28</sup> have defined the celiac disease as one in which there is an insidious onset with feces which are loose, bulky, pale, and foul; distention of the abdomen and wasting; and for which laboratory data include low blood sugar curve, "clumping" of barium meal in the roentgenograms, excess fat in the feces, and a low rise in vitamin A absorption test.

Low rise of vitamin A level after a standard test dose indicates defective absorption and is a constant feature of celiac disease and of fibrosis of the pancreas. The defect in celiac disease is in the ability of the intestinal mucosa to absorb vitamin A and fat. Deficiencies of A, C, and D result from the impairment of absorption rather than as the cause of the disease. The analysis of

pancreatic enzymes is normal in celiac disease.

When *mecholy* has been given, there is a normal blood sugar curve and no "clumping" but no change in the absorption of vitamin A if it is introduced intraduodenally. Absorption of vitamin A is not improved by the addition of bile salts, olive oil, and milk or by their introduction intraduodenally, when *mecholy* has been given. There is no improvement with the addition of pancreatin to the test meal intraduodenally.

The intramuscular injection of *crude extracts of liver* and the *B complex of vitamins* has been followed by improvement in the absorption of vitamin A in 3 to 6 weeks. Irregular results are obtained after the oral administration of these products. It is recommended that 2 to 4 cc. of crude liver extract be given intramuscularly every other day and 2 to 4 cc. of parenteral B complex every other day on alternate days and to continue the intramuscular administration until there is improvement and then to give them orally. The *diet* should be modified to skimmed milk, banana, curds, and scraped beef. *Vitamins A, C, and D* should be given in twice the usual amounts.

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## DIPHTHERIA

ROBERT A. LYON, M.D.

In the annual report<sup>29</sup> of the deaths from diphtheria occurring in large cities of the United States during 1941 the mortality rate was 0.56 per 100,000 population which represented 209 deaths in a population of over 37 million. There were 16 fewer deaths than in the previous year of 1940 and the rate was the lowest ever recorded. In 27 cities there were no deaths from diphtheria during

1940 or 1941 and in 40 cities there were no deaths during the year 1941.

A total number of 753 patients with diphtheria entered a Los Angeles hospital over a period of 16 years and a downward trend of incidence was noted during that period of time, but the case fatality rate remained about the same—approximately 5 per cent. These observations were reported by Y. Togasaki,

L. Rosove, A. G. Bower, and P. M. Hamilton.<sup>30</sup> Many of these patients (61 per cent) were less than 10 years of age and the average duration of the illness before antitoxin was 3.7 days. Bronchopneumonia was the most frequent complication, and others, in order of frequency, were toxic myocarditis, purpura, atelectasis, emphysema, otitis media, and hemorrhagic nephritis. In one instance a child who received a large amount of antitoxin intravenously reacted violently and died within 36 hours. It seemed probable that the serum reaction was responsible for this death.

Among a series of 100 patients suffering from postdiphtheritic carditis C. Neubauer<sup>31</sup> noted lesions of heart musculature, abnormalities of rhythm, and interference with normal conductivity. Among the arrhythmias, partial auriculo-ventricular block occurred in 17 per cent of instances and partial bundle branch block in 19 per cent of cases, complete auriculoventricular block in 5 per cent and complete bundle branch block in 4 per cent. Other less common arrhythmias were auricular fibrillation and ventricular tachycardia. Electrocardiograms gave evidence of some of these lesions for some time before severe collapse occurred. It seemed important to observe diphtheria patients for a period of at least four weeks when the attacks were mild and from six to seven weeks when the attacks were moderate and longer periods of time, possibly three months, when cardiac damage had occurred.

**Prevention**—The effectiveness of campaigns for the prevention of diphtheria has been studied<sup>32</sup> in England and Wales, where it was noted that only about one-third of the child population was receiving immunization against diphtheria. To determine the reason for the small percentage the committee devised

a questionnaire which was used for mothers of 25 different areas throughout England and Wales. A total number of 3860 replies were analyzed. It was found that 92 per cent of this group had heard of the diphtheria immunization; most of them (56 per cent) through school organizations, and 18 per cent from child welfare organizations. The remaining number had heard of diphtheria immunization from friends, private doctors, neighbors, radio, newspapers, public posters and films. The most effective sources of information seemed to have been the doctor, nurse and teacher working in schools, child welfare centers, in hospitals or private offices. More than half of the number of parents who had heard of immunization from one of these sources had followed the advice. Only 10 to 25 per cent of the mothers had been sufficiently impressed by information appearing in newspapers, public posters or films to have the immunization procedures carried out. Although only a small number of persons heard of diphtheria immunization from private physicians, this source of information was the most effective in producing results. The most common excuse given by parents for failure to carry out the procedure was illness of the child. About one-third of the group had good intentions but had not found a convenient time to avail themselves of the treatment. A group consisting of 24 per cent of the mothers were apathetic and another group of about 13 per cent had false ideas of the nature of the immunization and were fearful of reactions such as swollen arms or systemic illness. In some instances there was a confusion as to the purpose of the immunization—it was thought by some to be vaccination against smallpox. A number of parents were prejudiced against the vaccination, believing it to

be a useless procedure and that since the child was well, he did not need any such treatment. There was no definite opposition to the immunization procedure on the grounds of its causing harm. In summary, there seemed to be about half of the group who resisted the immunization procedure in some minor degree, and about 17 per cent who intended to have the immunization performed but were waiting for the clinic or the school to make the next move. In its general recommendations, the committee felt that there was no need for continuing the expenditure of money on posters, movies, and the like to publicize immunization, but that more direct contact of parents with the physician and nurse in the private office, welfare clinic, and school was necessary, not only to educate the family but also to provide more ready access to the treatment itself. The information which required publicity should include statements that smallpox vaccination and diphtheria vaccination are different, and that even the healthy child needs immunization. The father as well as the mother should be convinced of the need for prevention of diphtheria in their children and any information printed in leaflets should be concise and give definite instructions as to where and when the parents should take the child for the immunization.

The nationwide survey in the United States, reported by L. Baumgartner,<sup>33</sup> indicated that the general public was aware of the value of immunization procedures and offered no resistance to their application. More than half of the population requiring immunization were willing to take the necessary treatment, but they had inadequate knowledge of the number of injections necessary and the age at which they should be given.

Immunity of the newborn is dependent upon the immunity of the mother. In a series of two hundred mothers and infants tested by M. A. Brescia<sup>34</sup> it was found that 26 per cent of the mothers were Schick positive. The infants of these Schick positive mothers were positive in 52 per cent of the cases but by the end of four months all had become positive. The infants of 74 per cent of the mothers who were Schick negative were also negative up to the age of four months. After this period of time they gradually became positive until by the end of one year the great majority had lost their immunity. It was the opinion of the authors that the number of Schick positive mothers was increasing somewhat since the decline of incidence of clinical diphtheria, and if the baby is to be protected during the first month of life it would be necessary to immunize the mothers against diphtheria during pregnancy.

Concurrent immunization against tetanus, diphtheria and pertussis has been tried with various methods by J. J. Miller and T. M. Saito.<sup>35</sup> Tetanus and diphtheria fluid or alum-precipitated toxoid were used in conjunction with pertussis vaccine. The children varied considerably in respect to the amount of tetanus antitoxin they developed in the blood, and a few children failed to produce any antitoxin following the injection of fluid toxoid. Alum-precipitated toxoid proved to be a better antigen. Blood levels of tetanus antitoxin were higher when the interval between the injections was at least three months. These injections of the tetanus toxoid seemed necessary to insure adequate protection against that disease. Over 90 per cent of the children became Schick negative following the procedure and almost all of the children developed agglutinins to the pertussis bacilli which

remained in high titers for a period of at least one year. Higher levels of this agglutinin generally occurred when the diphtheria alum-precipitated toxoid was administered concurrently with the pertussis vaccine. A nonspecific response in the agglutinin titer occurred whenever toxoid was given, even though pertussis bacillus vaccine was not administered at the same time.

Mixed immunizations of diphtheria, tetanus and whooping cough have been carried out by J. H. Lapin.<sup>36</sup> At first separate injections of diphtheria toxoid, either fluid or alum-precipitated, and whooping cough vaccine were administered and the antibody responses of the patient were measured by the Schick test, the level of diphtheria and tetanus antitoxin in the blood, and the agglutination and complement fixation tests for the pertussis bacillus. There seemed to be no diminution in the antibody response of the patient when more than one vaccine was given at the same time. Some of the best responses in respect to antitoxin levels of diphtheria and tetanus were obtained when alum-precipitated pertussis vaccine and alum-precipitated diphtheria and tetanus toxoid were given simultaneously in three monthly injections. The reaction to these large combined injections was severe and one abscess developed. The author concluded that the best results and the

fewest reactions occurred when pertussis vaccine was administered first in three doses at monthly intervals followed by two injections of a combined tetanus and diphtheria toxoid given at two-month intervals.

The need for a third dose of tetanus toxoid several years after the initial injections was indicated from the observations of M. M. Peshkin.<sup>37</sup> He measured the antitoxin levels produced by tetanus immunization of 31 children and then observed the results of a third or booster dose given two years after the initial injections. Before this third injection the antitoxin titers were generally found to be dropping rapidly below the levels of immunity, but following the injection the antitoxin titers rose rapidly, reaching their maximum within seven days after the injection. The height to which they rose depended upon the previous level of antitoxin. Children who received only the initial injections often had inadequate antitoxin levels, while those who received the booster dose 3 to 15 months after this immunization had higher levels, but the best results were obtained in those who received the third injection after an interval of two years. Following the third injection about 25 per cent of the group had reactions consisting chiefly of elevations of temperature. In one instance urticaria had occurred.

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## ENDOCRINE DISTURBANCES

JOSEF WARKANY, M.D.

In the past year further progress has been made in the estimation of the urinary excretion of sex hormones in normal and abnormal children. Talbot, Butler, Berman, Rodriguez, and MacLachlan<sup>38</sup> reported on the urinary excretion of 17-keto steroids.

In Chart I were plotted as the ordinate the total neutral 17-keto steroids per 24 hours in milligrams against the children's ages as the abscissa. The black circles represent the values found in boys and the white circles those in girls. The shaded area defines the normal range. At



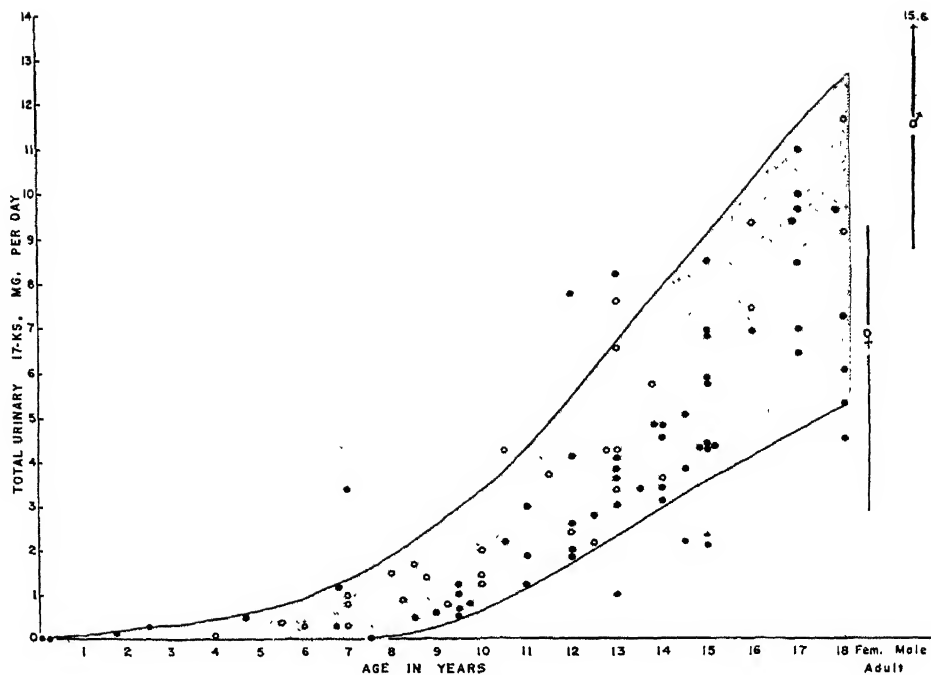


CHART 1  
EXCRETION OF 17-KETO STEROIDS BY NORMAL PERSONS. THE BLACK DOTS INDICATE  
VALUES FOR BOYS; THE CIRCLES, FOR GIRLS.  
(Talbot, *et al.*: Am. J. Dis. Child.)

the extreme right the ranges for adult males and females are indicated by vertical lines. Average values were calculated and presented in Table 1.

TABLE I  
AVERAGE OUTPUT OF 17-KETO STEROID PER DAY  
BY NORMAL PERSONS OF VARIOUS AGES\*

Age, Years	17-Ketosteroid Output, Mg.
3.....	0.15
4.....	0.3
5.....	0.4
6.....	0.5
7.....	0.65
8.....	0.95
9.....	1.4
10.....	1.9
11.....	2.6
12.....	3.4
13.....	4.3
14.....	5.3
15.....	6.3
16.....	7.2
17.....	8.1
Adult women.....	6.8
Adult men.....	11.0

\*Talbot, *et al.*: Am. J. Dis. Child.

From birth to eight years the total excretion of 17-keto steroids was below 1 mg. per day. During the period from 8 to 18 years, the average output rose from 1 to approximately 9 mg. per day. Normal children excreted at least 1 mg. per day after the age of 12 years. The day by day variations were relatively small so that a single determination of the 24-hour excretion was considered representative of one individual's output. In children showing advanced sexual development for their age without pathologic symptoms, the output of 17-keto steroids surpassed that of nine of every ten normal children of corresponding age. However, their excretion did not exceed the normal adult ranges. In dwarfs with developmental retardation due to anterior pituitary insufficiency the output of 17-keto steroids was abnormally low. The deviations in these cases were more evident in patients over 12 years of age. Excretion of 17-keto ste-

roids in obese children was within the normal or slightly above the normal limits for their respective ages. In patients with hypothyroidism who had been treated with thyroid the output of 17-keto steroids tended to be slightly low. No definite tendency to abnormal secretion was found in patients with mongolism. The amount of 17-keto steroids excreted by children with adrenal dis-

urinary excretion of the gonadotropins, estrogens, and 17-keto steroids which approached levels characteristic for adults. By means of these assays this physiological precocity may be differentiated from the precocity caused by hypertrophy or neoplasms of the adrenal cortex. Carcinoma especially gave rise to a high level of excretion of the estrogens and 17-keto steroids. Granulosa

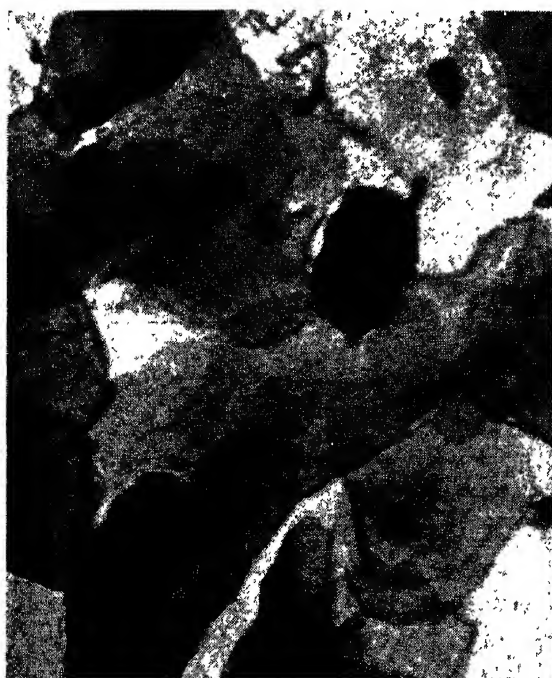


Fig. 1—Vaginal smear consisting of plaques of cornified epithelial cells (type IV). (B. B. Rubinstein: J. Clin. Endocrinol.)

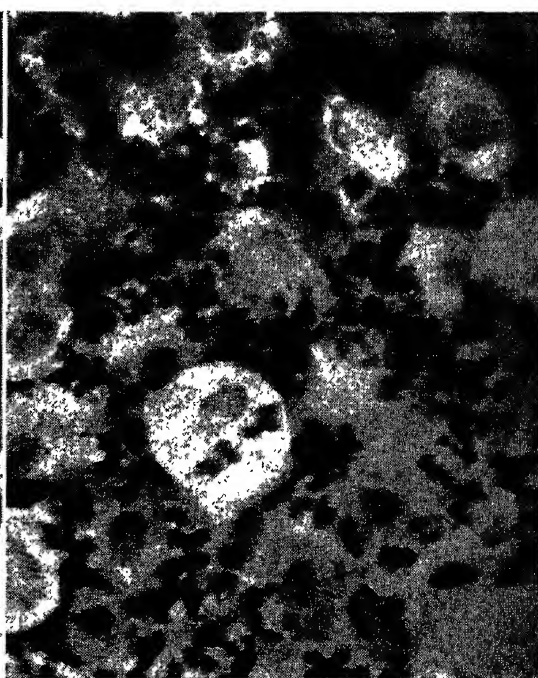


Fig. 2—Vaginal smear consisting of basal epithelial cells (type VIII), which are small round cells with large vesicular polychromatic nuclei. (B. B. Rubinstein: J. Clin. Endocrinol.)

orders deviated widely from the normal output (SEE: CYCLOPEDIA OF MEDICINE, SURGERY, AND SPECIALTIES, *Service Vol. 1943*, pp. 596-602).

Excretion of sex hormones in abnormalities of puberty was examined by Nathanson and Aub.<sup>39</sup> In addition to the 17-keto steroids, the pituitary gonadotropic hormone and the estrogens were included in this study. In precocious puberty not caused by neoplasms there was a moderate elevation in the

cell tumors of the ovary were associated with a greatly increased excretion of estrogens alone without change in the 17-keto steroids. Intracranial tumors with resultant precocious puberty sometimes caused excretion of amounts which fell within the range of those of children with physiological precocity. In patients with retarded growth and development the variations in the rates of excretion of various hormones depended upon which gland was primarily deficient.

Hypofunction of the anterior pituitary gland resulted in decreased levels of excretion of gonadotropic hormones, estrogens, and 17-keto steroids. Primary gonadal deficiency could cause an increase in the excretion of the gonadotropins, which are produced by the anterior pituitary, estrogens, and 17-keto steroids. In cases of adiposogenital dystrophy, pituitary gonadotropins were not recovered from the urine and the 17-keto steroids were diminished in the male, while the estrogens were decreased in the females of this type.

Menstrual disturbances in adolescent girls and their treatment were discussed by B. B. Rubenstein.<sup>40</sup> Such disturbances were usually temporary, but excessive or persistent bleeding required medical intervention. *Endocrine therapy* based on the results of vaginal smears was attempted by the author in cases of excessive bleedings. Hyperplastic epithelium was indicated by a vaginal smear consisting of plaques of cornified epithelial cells (type IV); the keratinization of the epithelium was caused by a persistent level of estrin; the proper treatment in such a case was administration of *progesterone*. Fifty milligrams of progesterone injected over a five-day period proved an effective therapy. In contrast to this form of bleeding, hypoestrinism started at the time of a normal menstruation but failed to stop, since there was a delay in reconstitution of the endometrium. The vaginal smears of such patients consisted of basal epithelial cells (type VIII, Fig. 2) which were small and round with large vesicular polychromatic nuclei. Estrogenic therapy which stimulated the proliferative and reparative processes in the endometrium was recommended for such cases.

W. A. Schonfeld<sup>41</sup> described the management of male pubescence. During

the period of prepubesence the testes do not grow but are maintained in a state of latency through the action of sub-threshold amounts of hypophysial gonadotropic hormones. The author defined pubescence as the period in which increased secretion of pituitary gonadotropic hormone causes stimulation of the interstitial cells of the testes, the production of androgenic hormones, and rapid growth of the penis, prostate, seminal vesicles, larynx, etc. The stage of development during which production of spermatozoa begins and the ability to procreate is established is called puberty. Continued development of the primary and secondary sex characteristics to full maturity constitutes the period of post-pubesence or adolescence. The author has studied in 1500 males selected at random the variations in age of the onset of pubescence, the rate of development, and the ultimate size of the genitalia. Pubescence was found to begin normally at any age from 10 to 16 years, although in isolated cases it may begin even later.

Cognizance of these normal variations assists in the proper understanding of many problems of pubescence. Prepuberal obesity or the pseudo-Fröhlich syndrome was not considered an "adiposogenital dystrophy" by this author, since the measurements of the penis and testes as well as the dates of onset of pubescence fall within the normal range. With the advent of puberty most of these boys grow taller and slimmer, although they maintain their characteristic somatotype through life. The terms "Fröhlich's syndrome" and "adiposogenital dystrophy" should be limited to cases of secondary eunuchoidism associated with obesity as a result of a craniopharyngioma or an inflammatory or degenerative lesion involving both the hypothalamus and the hypophysis. The treatment of Fröhlich's syndrome involves the *removal of the*

*primary pathologic process*, if possible, and *induction of pubescence with androgens*. In the differentiation of bilateral cryptorchism or delayed puberty from eunuchoidism the author used the therapeutic test of injecting large doses of gonadotropins. Evidence of response proves that the boy has at least one normal testis and probably adequate anterior hypophysial function. When deficiency of growth is associated with eunuchoidism, as proved by the fact that the genitals do not respond to large doses of gonadotropins, the treatment is directed toward the induction of pubescence by administration of androgens. This is usually associated with a spurt of growth. However, deficiency in growth during prepubescence is only rarely due to eunuchoidism. In cases of short, normal boys the pituitary growth factors are of no value. In acne and gynecomastia endocrine treatment has proven unsuccessful.

The effect of androgens on growth has been studied by various authors. Webster and Hoskins examined the effect of testosterone propionate on epiphyseal closure and linear growth in hypogonadal adolescent boys. It had been stated that administration of androgens accelerates epiphyseal closure and retards growth. The authors found that a reverse effect was taking place in the boys studied by them. The growth rate was markedly increased during periods of *androgen therapy* and roentgenograms of the knees, ankles, and wrists showed no evidence of epiphyseal closure. The administration of *testosterone propionate* in doses of 75 to 125 mg. weekly to eight hypogonadal adolescent boys ranging in age between 9 and 18 years was accompanied by an increase in average growth rate from 1.36 cm. per 100 days during the control period to 3.6 cm. per 100 days during the period of therapy. Following

the cessation of treatment the average growth rate again fell to 1.56 cm. per 100 days.

McCullagh and Rossmiller found a consistent gain in weight in patients treated with *methyl testosterone*. These authors reported a case of dwarfism who showed an approximate growth of one inch per year between the ages of 12 and 19 years. During this time he had received *desiccated thyroid* to tolerance and various other forms of treatment. During nine and a half months of almost continuous therapy with oral methyl testosterone this patient increased in height at the rate of 3.9 inches per year.

Wilkins, Fleischmann, and Howard studied the creatinuria induced by methyl testosterone in the treatment of dwarfed boys and girls. The administration of methyl testosterone caused retention of nitrogen which occurred within the first one to three days. Ten days after the beginning of treatment, an increase of the output of creatine occurred. This creatinuria continued to increase and was at a high level after two to five months of treatment. On discontinuing methyl testosterone a nitrogen equilibrium or deficit resulted within a few days, while the creatinuria decreased gradually over a period of 16 to 26 days.

Howard, Wilkins, and Fleischmann<sup>42</sup> reported also on the metabolic and growth effects of various androgens in sexually immature dwarfs. Hypopituitary dwarfs who failed to mature sexually and whose epiphyses remained ununited presented a special opportunity for the study of the influence of androgens upon growth and general metabolism. Eight dwarfed boys, most of whom were over 16 years of age, were treated with daily doses of 25 mg. of methyl testosterone by mouth for over one year. In addition to marked stimulation of sexual development, it was noticed that growth increased from an

average rate of one inch or less per year to about five inches per year. Osseous development progressed at a more rapid rate than previously, but there was no sudden closure of epiphyseal lines. The musculature increased in bulk and strength. Weight increased rapidly due to increased bulk of muscles, while there was no obvious change in subcutaneous fat. Marked elevation of the B.M.R. as high as plus 30 per cent occurred.

Two sexually infantile female dwarfs were studied. First they were given 1 mg. *diethyl stilbestrol* daily for periods of two to three weeks. Then they were given 25 mg. methyl testosterone in addition to the stilbestrol. Immediately a nitrogen retention occurred, followed later by marked creatinuria. One of these patients, a girl of 22 years, was treated in this way for over a year. Her face, figure, and personality changed from a child to a young woman. She grew moderately. No signs of virilization were noticed. In the other girl, treatment was discontinued after five months since the voice became a little husky and there was slight enlargement of the clitoris.

Cases of precocious puberty caused by tumors of the testes are rare in children. Werner, Spector, Vitt, Ross, and Anderson<sup>43</sup> reported a case of *pubertas precox* in a six-year-old boy which was produced by a tumor of the testis, originating probably in the interstitial cells. The patient was 5½ years old when abnormal growth of hair was noticed about the external genitals which were larger than normal. He had also frequent erections at this time. Hair began to grow in the axillae, on the lips, chin, and face. He was taller than normal for his age and his muscles were prominent and firm. His voice became deeper in tone. The mother asserted that he had smoked as many as 50 cigars since he was two

years of age without becoming ill. When seen at the age of six years and nine months his height was 53¾ inches, the normal height for his age being 45 to 48 inches. His weight was 73¾ lb., the normal being 42 to 52 lb. The penis, when flaccid, was 3¾ inches long and 1.5 inches in diameter. The left testicle was about 8 mm. in diameter and 1 cm. long. The right testicle was of the size of a medium-sized olive. The prostate was palpable, showed moderate development, and the consistency was soft.

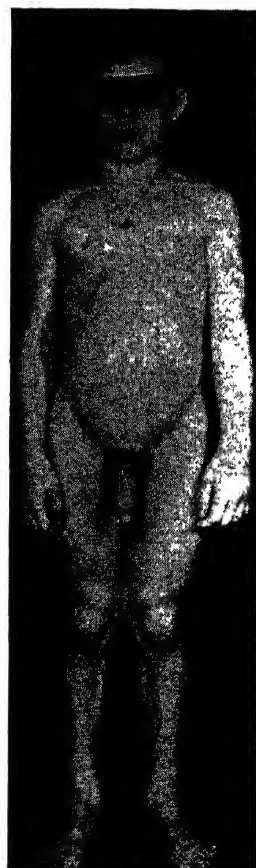


Fig. 3—Patient aged 6 years and 9 months. Note marked secondary sexual, skeletal, and somatic development. (A. A. Werner, H. I. Spector, A. E. Vitt, W. L. Ross, and W. A. D. Anderson: J. Clin. Endocrinol.)

The Friedman test of the urine for gonadotropins was negative. Basal metabolic rate was —14 and —15 per cent. The roentgenograms showed markedly advanced bone development. There were

no abnormal shadows over the renal or adrenal regions.

It was suspected that there was a tumor of the right testis and this gonad was removed.

The pathologist found that this testis measured 2.5 by 1.5 cm. Near one pole could be felt a nodule of firmer consistency than the surrounding tissue. Section through the long axis of the testis showed this firm area to be a yellowish gray tumor of roughly oval shape, and measuring 12 mm. in maximum diameter. The small tumor was situated just beneath the capsule of the testis, and protruded inward in such a fashion as to displace a considerable portion of the testicular tissue. The tumor nodule was quite circumscribed and appeared sharply separable from the testicular tissue.

The tumor tissue in its microscopic appearance was rather strongly reminiscent of the adrenal cortex because of the columnar arrangement, which was prominent in some areas, and because of the abundant, slightly granular cytoplasm of the individual cells. However, the cells had a morphology similar to the interstitial cells of the testis. The interpretation of the nature and origin of the tumor cells would seem to be that they were either adrenal cortical tissue or interstitial cells of the testis. Sections of the tumor were compared with those of interstitial cell tumors of the testis induced in mice by injection of stilbestrol. They were found to be closely similar. The weight of evidence suggests that the probable diagnosis is interstitial cell tumor of the testis. (SEE: Endocrinology, p. 63.

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## GENITOURINARY SYSTEM

WALDO E. NELSON, M.D.

### Pyelitis

The effects of various urinary antiseptics on strains of *Escherichia coli* have been studied by H. S. Helmholz.<sup>44</sup> Resistance to sulfathiazole was manifested by a small percentage of strains of *Esch. coli*. Strains resistant to *sulfathiazole* were also resistant to urinary acidity and to mandelic acid, but were more susceptible to *methenamine* and *methenamine mandelate* than were the non-resistant strains. *Sulfathiazole* and *sulfadiazine* seemed to be more effective against *Esch. coli* than *sulfacetimide*, *sulfapyridine*, or *sulfanilamide*. In concentrations of 0.5 mg. per 100 cc. sulfathiazole was more effective than sulfadiazine.

### Stones

Stones in the urinary bladder of children have been observed so infrequently

that symptoms which would cause one to suspect such a diagnosis in an adult may be overlooked in children. Seven cases occurring in children have been reported by R. B. Tudor.<sup>45</sup> Urinary frequency, dysuria, pyuria, and hematuria were the most common presenting complaints in this series, dysuria being present in each child. The symptoms of bladder stones usually were acute and well marked. This is due to the extreme sensitiveness of the mucous membrane and to the activity of the reflexes and, in part, to the pyramidal shape of the bladder, which causes the stone to gravitate to the trigone. Here it produces severe irritation and is frequently caught by the contracting muscular fibers, causing severe pain and sudden obstruction to the outflow of urine. Although the vesical stones in all of these patients were visualized on the

roentgenogram, diagnosis of stones in the bladder is not as certain as that of renal calculi. It has been estimated that only 50 per cent of vesical stones are visible on the roentgen film, while the proportion of renal stones which are not visualized is only 1.2 per cent. A cystogram made after injecting air often shows stones which are otherwise invisible, so that cystoscopy should be resorted to in all suspected cases in which the plain roentgenogram and the cystogram with injected air do not reveal the presence of stones.

### Vulvovaginitis

Favorable results in the treatment of gonorrheal vulvovaginitis with *silver picrate suppositories* has been reported by F. R. Fitch.<sup>46</sup> The treatment consisted of the daily insertion of one silver picrate suppository for a period of six days. This was followed by one day without treatment when a smear was taken before the use of the suppositories was resumed. This procedure was continued until the patient became free of symptoms and until there had been at

least six weeks' treatment after the last positive smear. Then the patient was placed on observation, with weekly smears for the first three months and smears once a month for the second three months. No patient was discharged until after at least six months' observation. If symptoms recurred or the smear became positive, the silver picrate treatment was resumed. The average duration of the initial treatment was 10.4 weeks. Thirty-two of the 57 children treated had relapses and were given a second course of silver picrate suppositories for an average of 9.8 weeks. Fifteen of this latter group had one or more additional relapses. In 42 per cent of the total group, the condition responded promptly and in 30 per cent more slowly. In 17½ per cent the treatment resulted failure, and in 10½ per cent the results were inconclusive.

It is the author's opinion that this treatment is second only to that of *sulfathiazole* and that it is the treatment of choice for children who do not tolerate sulfathiazole or are refractory to it.

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## HEART DISEASE IN CHILDREN

ROBERT A. LYON, M.D.

### Congenital Heart Disease

The *diagnosis* of congenital heart disease by visualization of the cardiac chambers and great vessels with an opaque substance introduced into a vein has been reported by M. L. Sussman, A. Grishman, and M. F. Steinberg.<sup>47</sup> They used a 70 per cent solution of diodrast and took roentgenograms in rapid succession as the substance coursed through the heart and great vessels (Figs. 4, 5, 6, 7). Prominence of the pulmonary artery was detected in patients with auricular septal defects, patent ductus arteriosus, pulmonary stenosis with dilated pulmonary ar-

tery, the Eisenmenger complex, and with idiopathic dilatation of the pulmonary artery. Enlargement of the right ventricle with a small pulmonary artery was found in isolated pulmonic stenosis with a small pulmonary artery, the tetralogy of Fallot, the trilocular heart with two auricles and one ventricle, and in cases of transposition of the great vessels with a small pulmonary artery. Left ventricular enlargement was found in coarctation of the aorta, aortic or subaortic stenosis, patent ductus arteriosus without dilatation of the pulmonary artery, idiopathic hypertrophy of the heart and in iso-



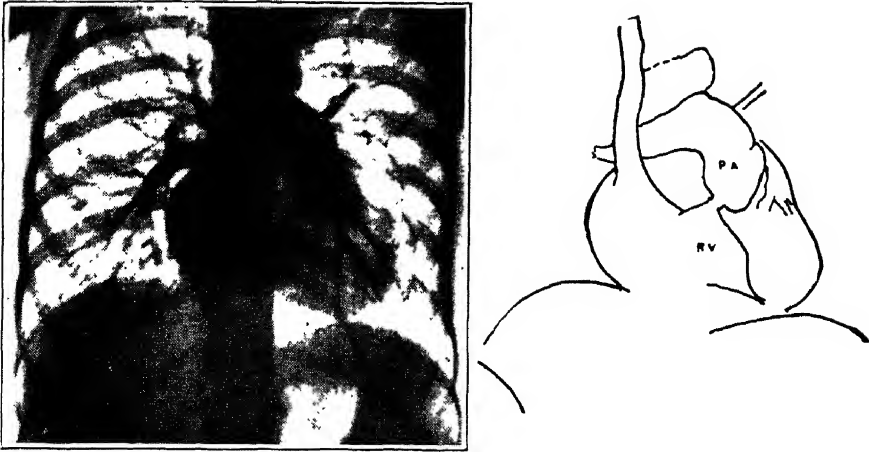


Fig. 4—Isolated pulmonic stenosis in a 7-year-old girl. Angiocardiogram (posteroanterior), made 2 seconds after injection, showed enlarged right side of the heart, stenosed pulmonic conus, and moderately dilated pulmonary artery. (M. L. Sussman, A. Grishman, and M. F. Steinberg: *Am. J. Dis. Child.*)

lated interventricular septal defects. The method of visualization was especially valuable in the detection of a persistent right aortic arch.

The abnormal shadows produced in roentgenograms by the various types of congenital heart disease have been reviewed by R. S. Bromer.<sup>48</sup> In interventricular septal defects the ventricles may be enlarged and occasionally the pulmonary conus is somewhat greater in

size but no characteristic change in the roentgenogram may be expected. Inter-auricular septal defects may produce great enlargement of the pulmonary conus or a large shadow to the right of the sternum probably because of the dilated right auricle. Pulmonary stenosis usually causes a diminution of the width of the shadows at the base of the heart. In the tetralogy of Fallot the same picture may occur with the sharp concave an-



Fig. 5—Patent ductus arteriosus (after ligation) in girl aged 12 years. Angiocardiogram (left oblique), made 7 seconds after injection, shows entire aorta. There is a bulge in the contour of the proximal portion of the aorta descendens anteriorly, which corresponds to the infundibulum of the ductus persisting postoperatively. Metal clips were placed adjacent to the ligated ductus at operation (Dr. W. S. Touroff). (M. L. Sussman, A. Grishman, and M. F. Steinberg: *Am. J. Dis. Child.*)

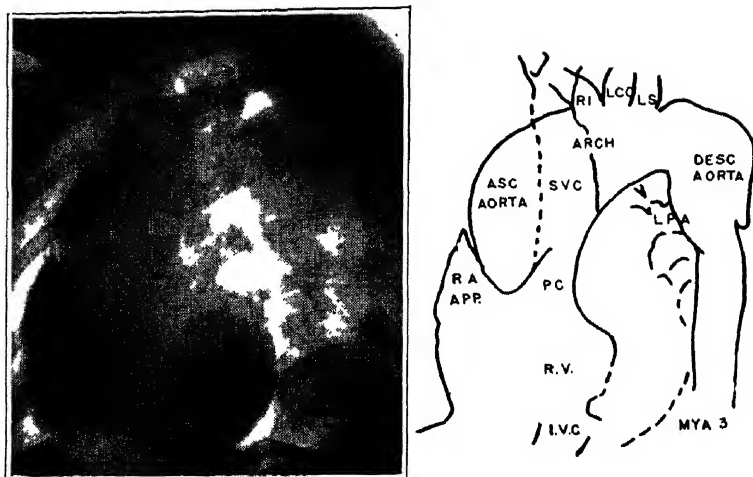


Fig. 6—Tetralogy of Fallot in a girl aged 9 years. Angiocardiogram (left oblique), made 2 seconds after injection, shows simultaneous visualization of right and left sides of the heart and of the aorta. The ascending aorta is dilated. The arch is deformed. The proximal portion of the aorta descendens is moderately dilated. The pulmonary artery is hypoplastic. (M. L. Sussman, A. Grishman, and M. F. Steinberg: *Am. J. Dis. Child.*)

gulation in the region of the pulmonary artery and the blunt apical shadow which produces the "woodenshoe" type of heart. Complete transposition of the great vessels may cause the enlargement of one ventricle or the other. Patency of the ductus arteriosus may cause either or both ventricles to enlarge and the pulmonary conus may be dilated. In the roentgenologic diagnosis of any of these

lesions, a great deal of assistance may be obtained by the use of the fluoroscope in oblique and lateral positions, and occasionally orthodiagrams and kymograms may add to the knowledge of the size and configuration of various portions of the heart (SEE: Figs. 8, 9).

The *circulation time* in infants and young children has been determined by the fluorescein method by C. M. Witz

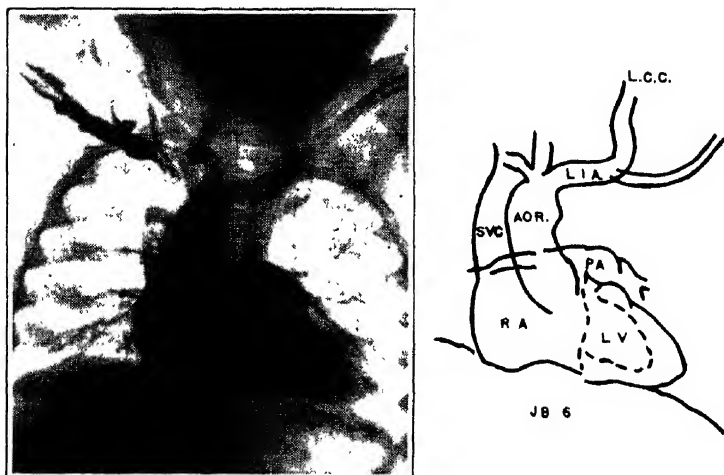


Fig. 7—Tetralogy of Fallot in a girl aged 4 years. Angiocardiogram (posteroanterior), made 3 seconds after injection, outlines the right and left sides of the heart and the aorta and pulmonary artery simultaneously. The pulmonary artery is small and the conus is stenosed. The aortic arch is dextroposed. The aorta descendens passes downward to the right of the spine. The innominate artery is to the left of the spine. (M. L. Sussman, A. Grishman, and M. F. Steinberg: *Am. J. Dis. Child.*)

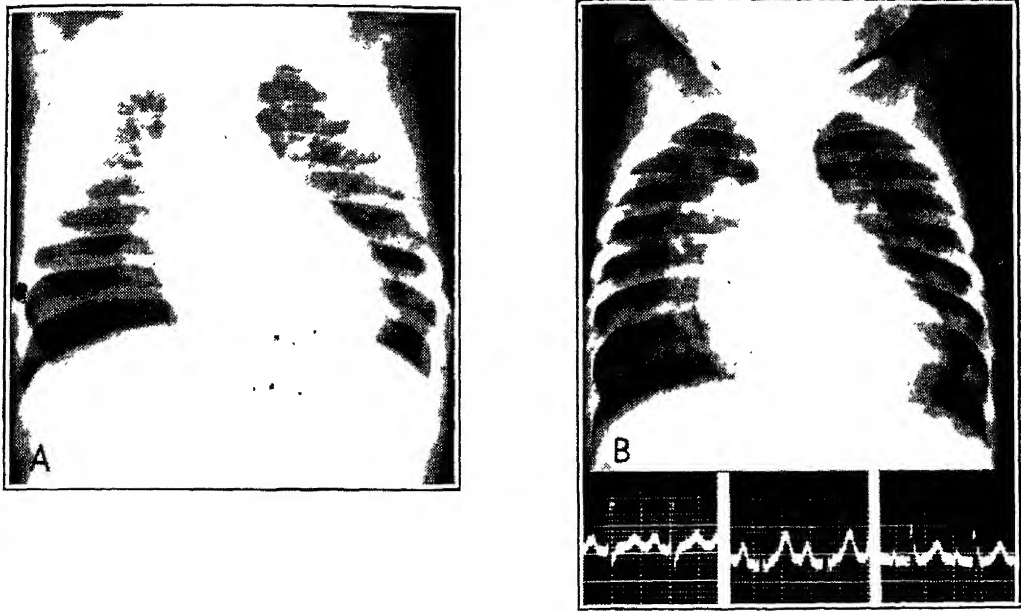


Fig. 8—Complete transposition of aorta and pulmonary artery associated with: *A*, Pronounced hypertrophy and dilatation of right atrium and right ventricle, hypoplasia of left atrium and left ventricle, patent foramen ovale; *B*, hypertrophied left ventricle about 5 times the size of the right, enlarged dilated right atrium, interventricular septal defect, 1.1 cm. in diameter. (R. S. Bromer: J. A. M. A.)

berger and H. G. Cohen.<sup>49</sup> The dose of fluorescein is 0.07 cc. per Kg. of body weight and is injected intravenously in an available vein in the hand or arm. With the lights out and an ultraviolet lamp directed at the subject, a green fluorescence can be noted on the lip when the drug reaches that site and the exact interval from the time of injection to the

appearance of the color can be determined. In 51 children between the ages of 3 and 13 years the average figures were 11.5 seconds, ranging from 7 to 16 seconds. In a group of 25 infants between the ages of 1 and 24 months the average time was 7 seconds with a range of 5 to 9.1 seconds. The method appears to be without danger, has a fairly ac-

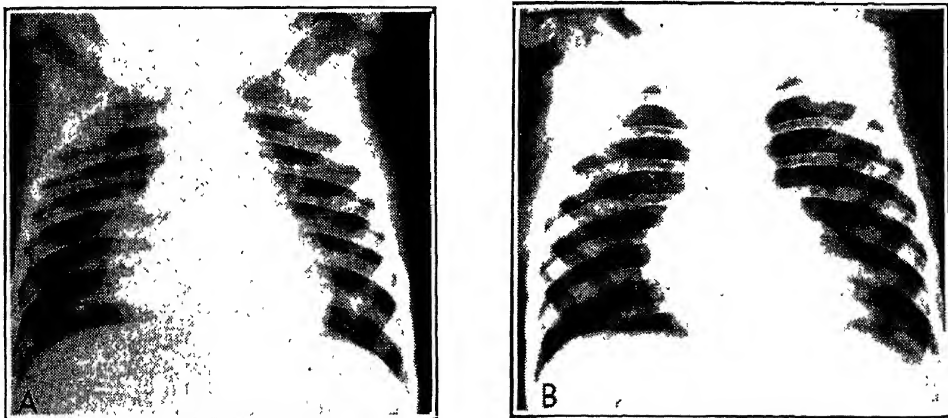


Fig. 9—Pulmonary stenosis: *A*, Stenosis of the pulmonary valve, dilatation of pulmonary artery distal to site of stenosis, rounded prominence in region of the pulmonic arc; *B*, hypoplasia of conus of right ventricle and of pulmonary artery. (R. S. Bromer: J. A. M. A.)

curate end-point for measurement, and is not influenced by the crying or struggling of the child.

### Complications

The incidence of acute and subacute bacterial endocarditis in congenital heart disease has been determined by R. Gelfman and S. A. Levine<sup>50</sup> from a review of 34,000 autopsies performed at various

than females in the older age group. Death occurred in 6 per cent before the age of two years and in 80 per cent before the age of 40 years. Fourteen per cent of the patients over two years of age had superimposed rheumatic infections. Interauricular septal defect was the most common congenital lesion in the group but it was not complicated by bacterial endocarditis. Endocarditis was found,

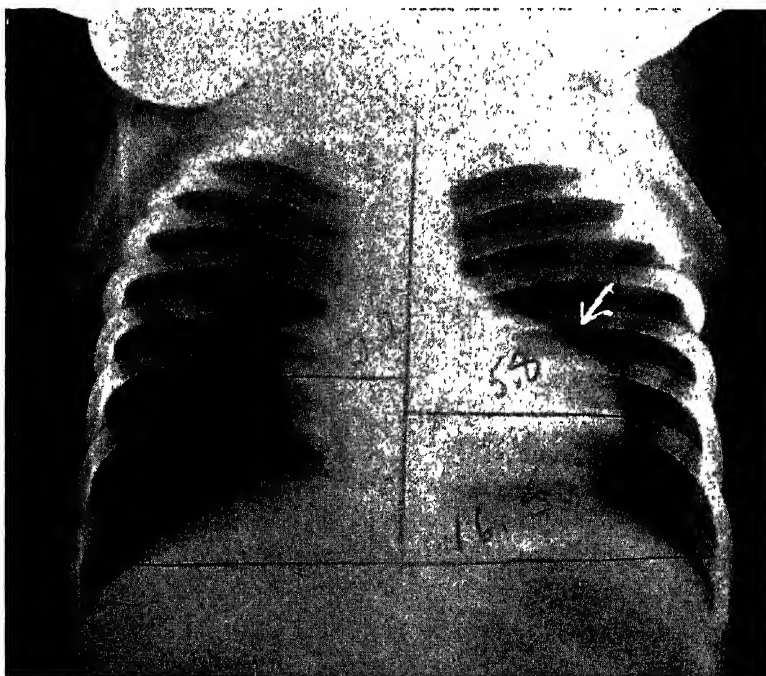


Fig. 10—(Group I.) Tetralogy of Fallot. Right border, 3.2 cm.; left border, 5.8 cm.; total transverse diameter, 9 cm.; internal diameter of chest, 16.5 cm. Note the sheep's nose. (P. W. Emerson and H. Green: J. Pediat.)

hospitals in Boston. Congenital cardiac defects occurred in 453 instances or 1.3 per cent of the total number of cases, but most of these were in infants less than two years of age. The incidence of congenital lesions in patients over two years of age was 0.5 per cent. Bacterial endocarditis occurred in 6.5 per cent of the total group of 181 patients with congenital heart disease but the incidence was 16.5 per cent of those over two years of age. The distribution of males and females in the total group was about equal in infancy, but there were more males

however, in 57 per cent of patients over two years of age who had interventricular septal defects, in 20 per cent of those with patent ductus arteriosus, and 21 per cent of those with bicuspid valves, 29 per cent with the tetralogy of Fallot, and 29 per cent with pulmonary stenosis. Bacterial infections were much less frequent in the patients who were less than two years of age.

A series of 46 patients who had some type of *transposition of the great vessels* has been reviewed by P. W. Emerson and H. Green.<sup>51</sup> These patients were

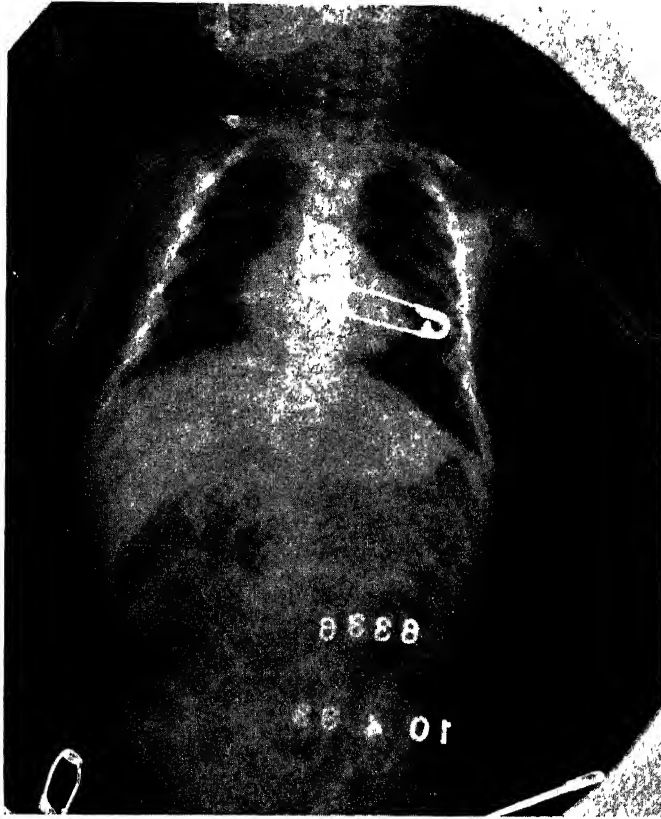


Fig. 11—(Group II.) Overriding aorta and pulmonic atresia. Note the transverse oval.  
(P. W. Emerson and H. Green: J. Pediat.)

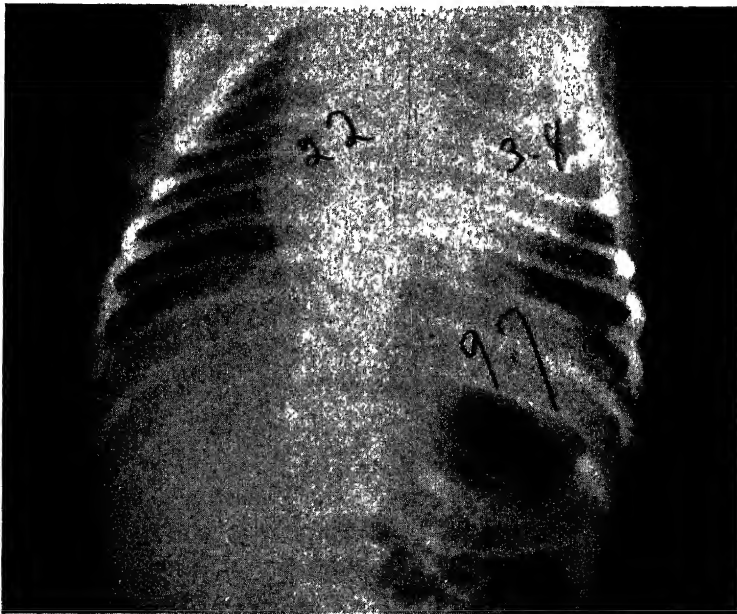


Fig. 12—(Group III.) Simple transposition of the aorta with coarctation and mitral atresia. Markedly enlarged and globular heart. Measurement, 2.2 by 3.4 cm. = 5.6 cm.; internal diameter of the chest, 9.7 cm. (P. W. Emerson and H. Green: J. Pediat.)

divided into five different groups. In the first group the aorta was shifted to the right so that it came to lie just over the interventricular septum and received blood from both ventricles. There were 11 patients with this sort of defect and an associated stenosis of the pulmonary valve. Eight of these had the other findings typical of the tetralogy of Fallot and the diagnostic feature was the cardiac shape in the roentgenogram. The enlarged right ventricle and right auricle, and the diminished size of the shadow of the pulmonary artery produced a cardiac shape resembling a sheep's nose, or a wooden shoe. In the next group of patients the aorta overrode the interventricular septum and the pulmonary artery was atresic. Occasionally the pulmonary artery was atresic without any abnormality of the aorta's position. In roentgenograms the heart often assumed a transverse oval shape which sometimes aided in the diagnosis but was not pathognomonic of the lesion. The symptoms of these first two groups of patients were the same and consisted of cyanosis which was present at birth, retarded growth, clubbed fingers, and dyspnea. In the third group of patients the aorta had rotated to such an extent that it arose from the right ventricle together with the pulmonary artery. There were eight patients of this type and most of them had other types of congenital defects. Cyanosis and dyspnea occurred in all, and death took place within a month or two after birth. A roentgenogram taken in one patient showed a globular-shaped heart. In the fourth group of patients the pulmonary artery arose from the left ventricle and the aorta from the right ventricle. Cyanosis, dyspnea, and retardation of growth occurred in all patients, and murmurs were heard in the majority of the group but not in any typical location. In roentgenograms

either one or both ventricles were enlarged. In the fifth group, comprised of seven patients, the great vessels were transposed and the tricuspid valve was also transposed so that it came to lie within the ventricle. The same symptoms of dyspnea, cyanosis, slowness of growth and development were noted in this group as in the others. The heart was generally enlarged but the murmurs were not typical in quality or in location. In roentgenograms of two or three of these patients there was a conspicuous bulge in the right upper part of the cardiac shadow, probably representing the bulge of the transposed aorta, and a straight vertical line below it which was probably the border of the right ventricle.

The course of three children with *coarctation of the aorta* and a review of the literature have been reported by P. H. Rhodes and E. Durbin.<sup>52</sup> A total number of 47 cases with this condition under the age of 15 years have been recorded in the literature. Common diagnostic signs have been forceful pulsation visible in the suprasternal notch and along the course of the subclavian and carotid arteries. The pulsation of the femoral vessels was weak and usually occurred slightly later than that of the radial pulse. The vessels of the retina have been reported to be tortuous and constricted. Collateral circulation which was noted infrequently in children consisted of visible or palpable blood vessels over the back in the scapular area. It was noted in one child as young as three years. Blood pressure readings have always been of assistance in reaching a diagnosis because of the elevation of the pressure in the arms and a lower pressure in the legs. Since the coarctation is often in the region of the origin of the left subclavian artery or between the left carotid and the left subclavian artery,

the blood pressure in the left arm may be lower than in the right. If only one blood pressure measurement is made the right arm should be used. In roentgenograms the defect in the aortic arch may be noted in the left anterior oblique position. Erosion of the ribs does not often occur in children although it has been noted in a child of only five years of age.

tion should be made as early as possible so that the few available measures for the prevention of complications can be instituted as soon as possible.

**Treatment**—The question whether the *ligation of a patent ductus arteriosus* does not involve a greater risk for the patient than if he were untreated has been raised by M. G. Wilson and

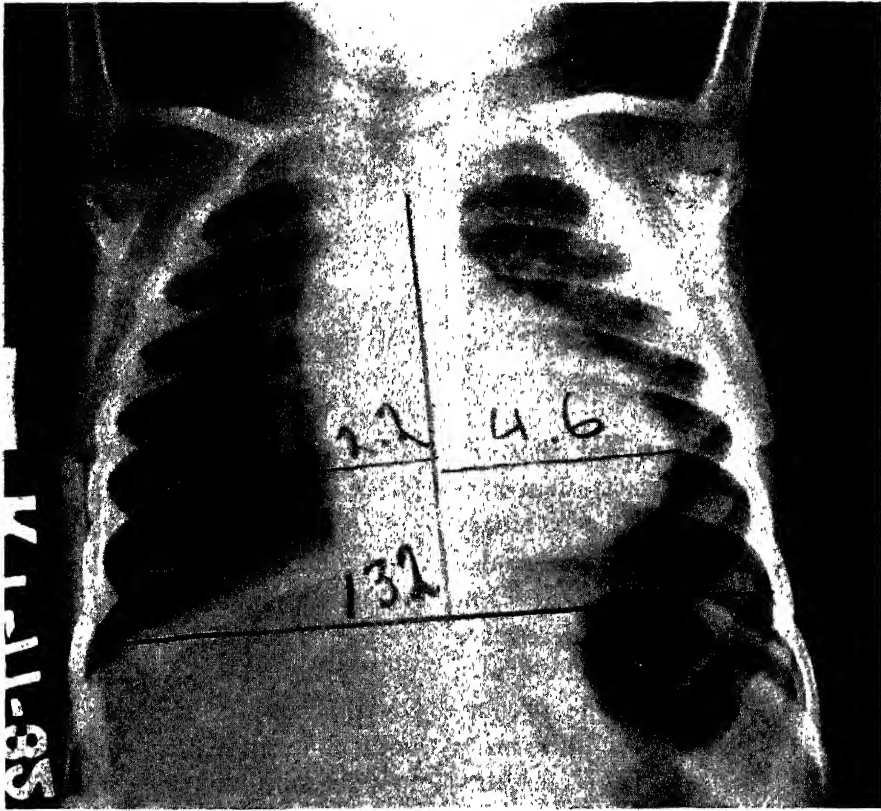


Fig. 13—(Group V.) Mixed transposition of the great vessels with transposition of the tricuspid valve. Note the bulge in the right upper portion of the contour due to the transposed large aorta. Note beneath this the short, almost vertical, border of the right ventricle. (P. W. Emerson and H. Green: J. Pediat.)

The left ventricle may be enlarged and the electrocardiograms may demonstrate a left axis deviation. The prognosis is uncertain. The authors found reports of several young adults who had met sudden death following strenuous exercise. Bacterial endocarditis, however, seemed to be a more frequent complication. Because of the possibility of these two forms of death the diagnosis of coarcta-

R. Lubschez.<sup>53</sup> In a review of 132 patients with congenital heart disease observed for an average period of nine years, they found that the cyanotic types of heart disease had higher death rates and shorter life expectancy than the acyanotic type, as represented by uncomplicated patent ductus arteriosus. There were 38 patients in their series who had patent ductus arteriosus as the only le-



sion and none of them had died from bacterial endocarditis or cardiac failure. One other such patient had died suddenly from an unexplained cause. In this group there were 24 patients who were now between 10 and 20 years of age; 12 between 20 and 30 years of age, and two who were over 30. In view of the low mortality rate in this group of patients, it seemed questionable whether routine operation during childhood should be undertaken.

The conclusion was reached by J. P. Hubbard<sup>54</sup> that the patients who had evidence of circulatory embarrassment were the ones needing the operation most urgently and that others who had no signs of lack of compensation might be observed carefully without operation. Evidence of circulatory embarrassment included enlargement of the heart which would consist of hypertrophy or dilatation of both ventricles; a low diastolic blood pressure with a greater than normal pulse pressure; signs of pulmonary congestion, and, finally, a retardation of growth and development. Each patient must be judged individually to determine whether the ductus is large enough to permit the shunting of a large proportion of arterial blood into the pulmonary artery and thus throwing a greater burden on the heart and circulation, or whether the opening is so small that little disturbance of blood flow takes place. The possibility of preventing subacute bacterial endocarditis by the ligation of the ductus has been suggested but it is too early to determine the prophylactic value of the operation.

In patients with *paroxysmal tachycardia* the impulses may arise in the auricle, in the auriculoventricular node, or in the ventricle. In a survey of the subject by W. D. Alsever,<sup>55</sup> reports of the management of 15 patients with auricular paroxysmal tachycardia were

summarized and the course of another patient observed by the author was given in detail. The first type of treatment to be tried in patients with this condition is the *stimulation of the vagus nerve* by pressure over the carotid sinus or over the eyeball. Occasionally the patient may obtain a vagal response by vomiting, by holding his breath, compressing his thorax, or possibly by lowering his head. The second form of treatment is *sedation*, which is possibly of value in children who are emotionally unstable or are easily aroused by environmental factors to fits of anger or fright, or are disturbed by the unnatural heart action. Paralysis of the sympathetic nervous system by *injection of the stellate ganglia* has been suggested as a form of therapy. *Mecholyl* has been one of the substances injected into the sympathetic fibers for this purpose. The fourth method of treatment is the use of *quinidine sulfate*, which most authors have found to be the best drug for restoring the normal cardiac rhythm. Quinidine sulfate is administered to adults in doses varying from 0.2 to 0.65 Gm. (3 to 10 gr.) but much smaller amounts are given to children. It is always best to start with an exceedingly small dose at first to determine the degree of the patient's sensitivity to the drug but after that it may be increased rapidly because it is eliminated quickly and has no cumulative effect. In the case of a 2½-year-old child reported by the author quinidine was administered in doses of 0.1 Gm. (1.5 gr.) at four-hour intervals, but when no effects were noted the dosage was increased to 0.3 Gm. (4.5 gr.) every four hours. After a total of 28 grains had been given the normal rate and rhythm were restored.

*Mecholyl* is sometimes successful in the treatment of this disease but it is such a powerful stimulant of the para-

sympathetic nervous system that dangerous reactions may occur. Some of this toxic effect may be controlled by the administration of *atropine sulfate*.

*Digitalis* has also produced good results in many cases of auricular paroxysmal tachycardia. It may be given in regular dosage although infants and young children may require more than the calculated dosage to secure maximum benefits from the drug. The author suggests the use of quinidine sulfate first because the rapid action of that drug may give immediate relief. If it is ineffective, digitalis should be employed.

### Rheumatic Fever

**Etiology**—An intensive study of the familial epidemiology of rheumatic fever has been undertaken by M. G. Wilson, M. D. Schweitzer, and R. Lubschez.<sup>56</sup> It would seem from their observations that there are children who are definitely predisposed to rheumatic fever because of hereditary factors. The nature of this susceptibility is of course unknown but the authors considered the possibility of some abnormalities of structure of the body tissues or some physiologic characteristics which responded to the rheumatic diathesis. Such children usually develop the first evidence of the disease at the average age of six years. The factors which initiate the response to rheumatic disease may or may not be bacterial in nature. The other children who are hereditarily immune to the disease escape the manifestations even though they are living or exposed in the same environment as the other children. There were no characteristics of the disease which would indicate that it was communicable in nature.

A relationship between poor diets and susceptibility to rheumatic fever was suggested by the studies of A. F. Coburn and L. V. Moore.<sup>57</sup> An analysis was

made of the diets of three groups of children, the groups differing in respect to economic status and the incidence of rheumatic attacks but not in respect to their possible exposure to streptococcus infections. The diets of the more susceptible and less susceptible children did not differ significantly in respect to caloric intake or quantity of phosphorus or thiamin, riboflavin, ascorbic acid, or vitamin D. The susceptible group were, however, receiving less protein, calcium, iron, and vitamin A than the less susceptible group. When some of the children of a cardiac convalescent home were given diets reinforced by two boiled eggs and two additional egg yolks, the incidence of rheumatic attacks was less than ordinarily would be expected. In the authors' opinion there were three factors which influenced an individual's susceptibility to rheumatic fever. One is an hereditary factor; another, exposure to specific hemolytic streptococci, and the third a nutritional element which "conditioned" the host to the infection.

**Diagnosis**—Changes in the size of the heart occurring in patients with rheumatic fever have been observed over a period of time by J. D. Keith and M. Brick.<sup>58</sup> The heart size was determined by comparisons of the transverse diameter with the chest width and by measurements of cardiac area by means of a planimeter. A series of 100 patients were studied with serial roentgenograms taken throughout the course of their rheumatic fever. In this group of patients 33 hearts became larger during the period of observation, 18 remained unchanged, and 49 became smaller. It was much easier to observe changes in heart size by roentgenograms than by physical examination. Changes in size took place slowly but could be detected after intervals of five or six months. Rapid changes did not occur unless pericarditis developed and

cardiac enlargement took place more readily when there was bradycardia rather than tachycardia. Rest in bed seemed to decrease the size of the heart. Continuous observation of heart size seemed to be of more importance in diagnosis and prognosis than the determination of types of murmur and valvular disease.

**Prevention** — The administration of *salicylates* to rheumatic patients has been tried by A. F. Coburn and L. V. Moore<sup>59</sup> as a means of preventing recurrences of the disease. In a group of young rheumatic patients cultures of the throat secretions were taken at the onset of every respiratory infection. When a Type A hemolytic streptococcus was recovered the patient received a daily dosage of 4 to 6 Gm. (60 to 90 gr.) of sodium salicylate for a period of four weeks. If this type of organism did not occur in the cultures the patient received no treatment with salicylates. In no instance did the latter group of patients develop recurrences of rheumatic fever. The 47 patients who had the Group A streptococcus associated with a respiratory infection were treated with the *sodium salicylate* and all but one escaped any recurrence of rheumatic fever. In another group of 139 untreated patients who had this same type of streptococcus associated with respiratory infections, 57 developed rheumatic recurrences and 82 escaped. Evidence that the salicylate therapy may have a real effect in preventing the rheumatic recurrence rather than merely masking the symptoms was the rapid decline in the erythrocytic sedimentation rate and the absence of other signs and symptoms of rheumatic disease.

Some recrudescences of rheumatic fever were prevented by the prolonged use of *sulfonamides* in the patients ob-

served by A. E. Hansen, R. V. Platou, and P. F. Dwan.<sup>60</sup> For a period of four years they observed 64 different children, the majority of whom received *sulfanilamide* regularly and others received *sulfathiazole* or *sulfadiazine*. A group of 32 patients comparable in age, sex, and stage of cardiac involvement served as a control group. Throughout the period of observation careful records were kept of infections of the respiratory tract, the type of organisms found in throat cultures, the trend of the leukocyte counts, and sedimentation rates. Electrocardiograms and roentgenograms were secured regularly every six months. During the first three seasons only ten of the group of 25 control subjects escaped without some sort of rheumatic recrudescence. In 20 patients receiving sulfonamide drug during the same period of time only one had a recrudescence of that disease. Later, more patients were added to the study so that a total of 53 received the sulfonamide and only two developed polyarthritides, but in one patient the attack occurred within six days after the treatment was started, so that he probably did not logically belong in this group. Of the 32 children in the control group 17 had recrudescences. The number of respiratory infections and the average gain in weight in these two groups was approximately the same, but the condition of the heart as judged by its size and by circulatory function was much better in the treated group. The amount of drug given during the first two years varied from 2 to 3 Gm. (30 to 45 gr.) daily but subsequently smaller amounts were given, generally 0.65 Gm. (10 gr.) with breakfast and the same amount with the evening meal. Reactions were infrequent. Rashes occurred in four instances, gastric disturbances in five, transient leukopenia as low as 4000

or less in several instances, but in one patient the count reached 1700 and the drug was discontinued. Sedimentation rates were generally lower in the treated group than in the control series. The authors were convinced that the prophylactic use of sulfonamides was of value but cautioned against their administration unless the child could be under the continual care of a physician and observed frequently throughout the period of treatment.

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## MEASLES

**Prevention**—A group of 255 children have been inoculated with measles virus which has been attenuated by three to 66 passages through egg embryos by J. Stokes, Jr.; G. C. O'Neil; M. F. Shaffer; G. Blake, and E. P. Maris.<sup>61</sup> The majority of these children had been under observation since birth and had not had measles previously. The attenuated virus was administered by intranasal instillation or by aerial spray which was inhaled by the patients or by intracutaneous injection. After incubation periods which were often slightly shorter than customary in regular measles, signs of measles developed. Many children developed coryza, fever, Koplik spots, and mild rashes. Cough and malaise were rare, and the fever was of short duration. None of the children were severely ill. Several susceptible children who were exposed to these patients contracted mild forms of measles similar to that produced by inoculation of egg-passage virus. This indicated to the authors that the passage of the attenuated virus through one human subject did not enhance its virulence. Once the virus had become attenuated by passage through

eggs, successive passages did not greatly vary its potency, although it was difficult to measure accurately the strength of the virus by animal inoculation methods. No difference in the type of measles produced in susceptible children could be noticed when virus from the third to eleventh passage was used or when virus from additional passages up to 66 was used. The route of administration, by nose drop, nasal spray, or intracutaneous injection did not affect the success in transmitting mild forms of the disease. Dilution of the virus did not affect the results and drying or freezing of the virus did not influence the potency.

The protection afforded by attenuated measles has been observed by E. P. Maris; G. Rake; J. Stokes, Jr.; M. F. Shaffer, and G. C. O'Neill.<sup>62</sup> A group of 22 children who had been inoculated were exposed by chance to measles and 15 escaped infection, four developed mild attacks, and three had typical measles. A group of 24 children who had been inoculated were given injections of blood from measles patients and 13 escaped infection, eight had very mild attacks, and three developed typical measles. As a summary of both groups, it might be said that 40 of a group of 46 children had received protection from the inoculation with virus attenuated by several passages on chick embryo membranes.

The virus of measles has been isolated for the first time from the brain of a patient with fatal encephalitis by M. F. Shaffer, G. Rake, and H. L. Hodes.<sup>63</sup> On the fourth day after the onset of the rash, symptoms of encephalitis developed in a boy seven years of age and on the ninth day death occurred. Suspensions of the brain material were injected into monkeys and the animals developed symptoms of measles.

Sulfathiazole was found by H. Gibel and A. M. Litvak<sup>64</sup> to be of little value in the treatment of measles and its complications except in reducing the mortality from bronchopneumonia. During an epidemic of over 1200 cases of measles, one-half of the group were treated symptomatically and the other half received  $1\frac{1}{2}$  grains of sulfathiazole per pound of body weight during the first 24 hours after admission to the hospital and one grain per pound of body weight every 24 hours thereafter until the patient was discharged. However, the patients who developed bronchopneumonia were given the drug, regardless of the group to which they belonged. The drug had no effect in reducing the duration of fever and the incidence of complications, but the mortality rate from bronchopneumonia was reduced to 1.85 per cent as compared with average mortality rate of 11.9 per cent in preceding years. The drug caused no unfavorable reactions and the leukopenia associated with measles seemed to be no contraindication to its administration. The authors concluded that it was unnecessary to treat every patient with sulfathiazole and its use should be restricted to the treatment of complications, especially bronchopneumonia.

**Complications** — Encephalitis complicating measles has been observed in 56 patients by A. M. Litvak, I. J. Sands, and H. Gibel.<sup>65</sup> From a review of the literature and from their own experience they estimated that the incidence of encephalitis in measles patients varied from 1 in 1000 cases to 1 in 1300. The onset of symptoms occurred at various stages of the measles; in a few instances before the first symptom of measles; in others before the development of the measles rash, but most frequently four to six days after the rash appeared and occasionally as long as 21 days after.

The symptoms sometimes occurred abruptly with convulsions, coma, and high temperature, or in other instances more gradually with listlessness, drowsiness, stupor, and coma. Rarely the onset was marked by signs of irritability, restlessness, and confusion. The incidence was greatest between the fourth and eighth years of age with one child less than three years of age and one as old as 16 years. There seemed to be no correlation between severity of the measles and the development of the complications. The prognosis varied. In the total series of 56 patients, eight died, a mortality rate of 15 per cent. Of the 32 patients who were followed in later months and years, 22 had sequelae, or 69 per cent.

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## MUMPS

*Surgical treatment* of severe orchitis complicating mumps has been advocated by C. Wesselhoeft and S. N. Vose.<sup>66</sup> When the operation was performed early, it not only gave relief from pain but saved the testicle from atrophy. The treatment should be started early when the first swelling is noticed. At this time the testicle is hard and swollen, and the scrotal tissues thin. With the first incision through the scrotal tissues fluid was released and then a cross incision was made in the membrane covering the testis. If there were inflammatory lesions elsewhere in the body the temperature dropped rapidly and immediate relief from pain was secured. In nine cases operated upon by the authors and followed for six months to a year later the results were favorable in all but one instance. In that case the operation seemed to have been performed too late to prevent atrophy of the testis. In untreated patients the incidence of atrophy was approximately 55 per cent.

## NEWBORN

### Congenital Anomalies

Congenital malformations could be made to occur regularly in the offspring of rats by feeding them diets deficient in various factors and the anomalies could be prevented by the addition of liver to the maternal diet. These experiments have been conducted by J. War-

vent all deformities. If this food was added to the diet at any time up to the thirteenth day of gestation, it prevented deformities in the offspring. The normal gestation period of the rat is 22 days.

Cleft palate was one of the deformities occurring in the rats fed on deficiency diets in the work of J. Warkany, R. C. Nelson, and E. Schraffenberger.<sup>68</sup> The

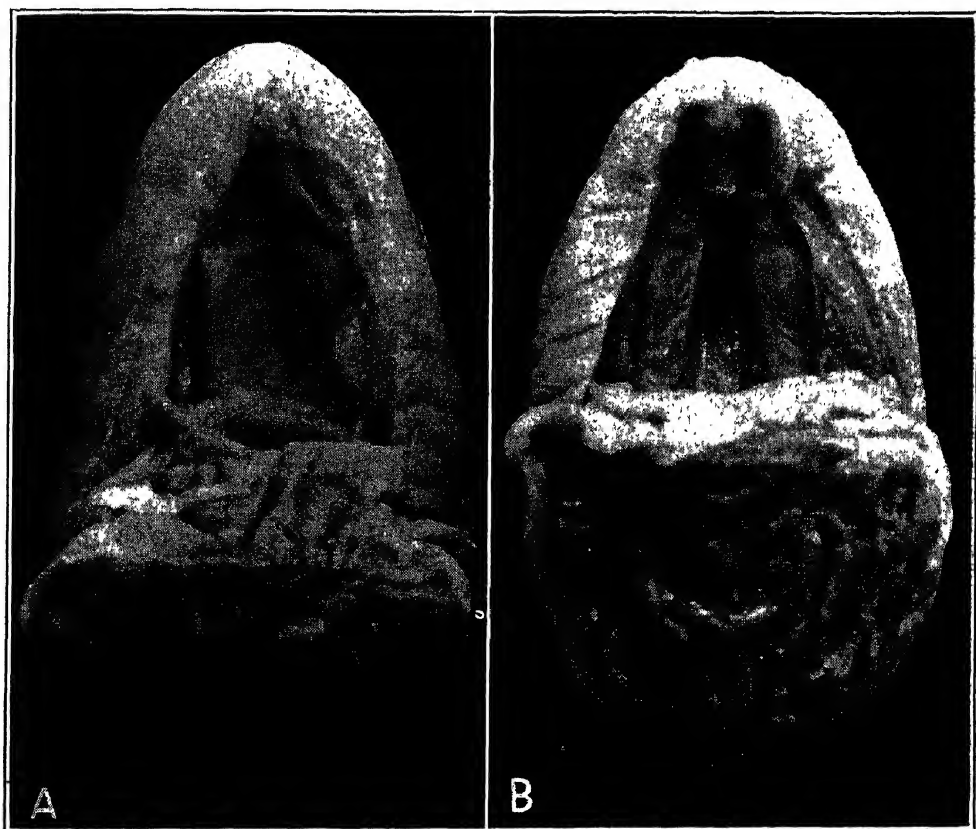


Fig. 14—A, Normal palate of newborn rat. B, Cleft palate. (J. Warkany, R. C. Nelson, and E. Schraffenberger: *Am. J. Dis. Child.*)

kany, R. C. Nelson, and E. Schraffenberger.<sup>67</sup> Several additions to the deficiency diet have been made to determine which type of food or mineral prevent the deformities. Iodine was added without effect in decreasing the number of congenitally malformed rats, and manganese, 10 per cent casein, 2 per cent alfalfa meal, and cod liver oil were likewise ineffective. Two per cent dried pig liver or an alcoholic extract of liver did pre-

authors emphasized the fact that these experiments proved that disturbances of fetal development could be brought about by environmental factors, such as modifications of diet as well as by genetic mutation (SEE: Figs. 14, 15, 16, 17, 18).

### Infections

*Osteomyelitis* of long bones occurred during the neonatal period in four infants observed by S. Stone.<sup>69</sup> The com-



mon symptoms were swelling of the affected extremity and diminished motion. Fever and other systemic symptoms were mild. Roentgenograms demonstrated the lesions and the treatment consisted of incision and drainage. In one instance a

Hemolytic colon bacilli have been suggested as the cause of some epidemics of *diarrhea* in the newborn by W. B. McClure.<sup>70</sup> Such organisms were isolated from the stools of infants of several hospitals in which epidemics of the disease

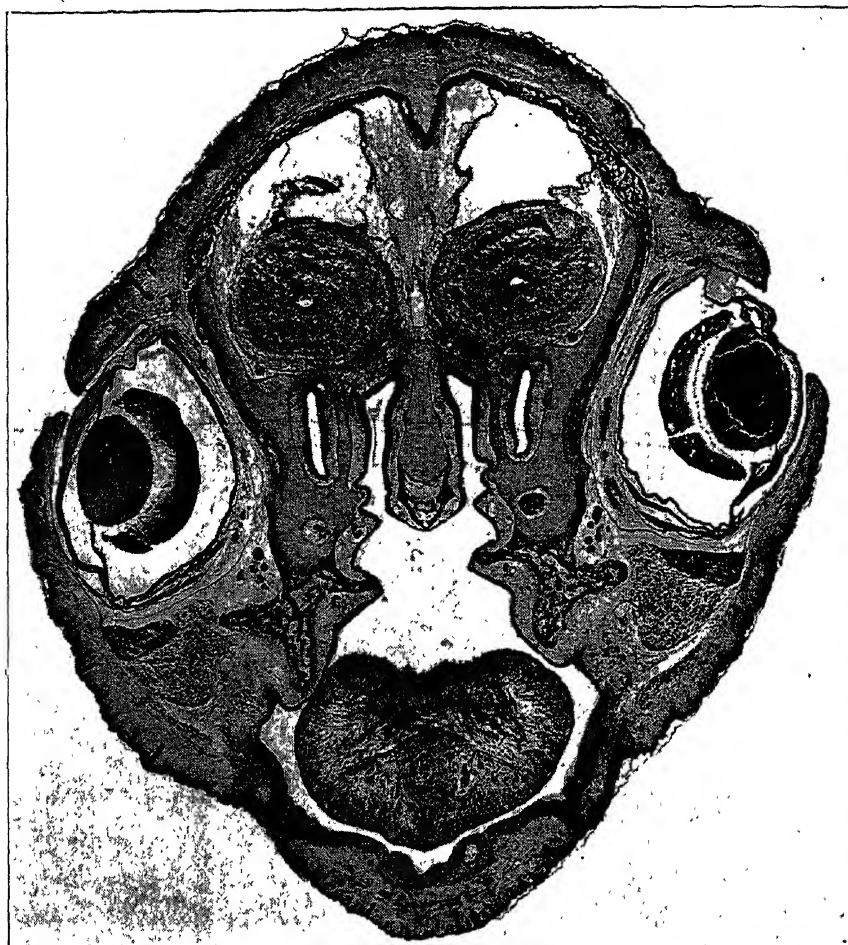


Fig. 15—Transverse section of head of newborn rat, with cleft palate, showing communication between nasal and oral cavities. (J. Warkany, R. C. Nelson, and E. Schraffenberger: *Am. J. Dis. Child.*)

*Streptococcus viridans* was the causative agent and in the other three patients *Staphylococcus aureus* was isolated. The reason for the mildness of these infections at this age period was thought to be the good blood supply and the thinness of the structures so that rupture of the abscess and drainage occurred readily and any necrotic bone caused by the infection was rapidly absorbed.

had occurred. They occurred with greater frequency in the sick than in the well infants of the same nurseries. Under conditions of partial carbon dioxide tension these bacilli produced soluble toxins which occasionally caused symptoms of diarrhea and vomiting when injected into cats. When cats were fed cultures of the organisms, a certain number developed diarrhea. The author emphasized the



danger of handling complementary feedings in close proximity with the place where infants were bathed and diapers were changed.

Western *equine encephalomyelitis* has been noted in newborn infants by H. Medovy<sup>71</sup> during a recent outbreak of the disease which occurred in Manitoba, Canada. Among a group of 509 patients,

ing signs were rigidity and opisthotonos. The cerebrospinal fluid contained an increased amount of protein and the number of cells varied from 100 to 1400. One of the week-old patients developed a spastic diplegia and cortical atrophy, and the other became microcephalic. A good many of the patients who had this type of encephalitis developed spasticity in

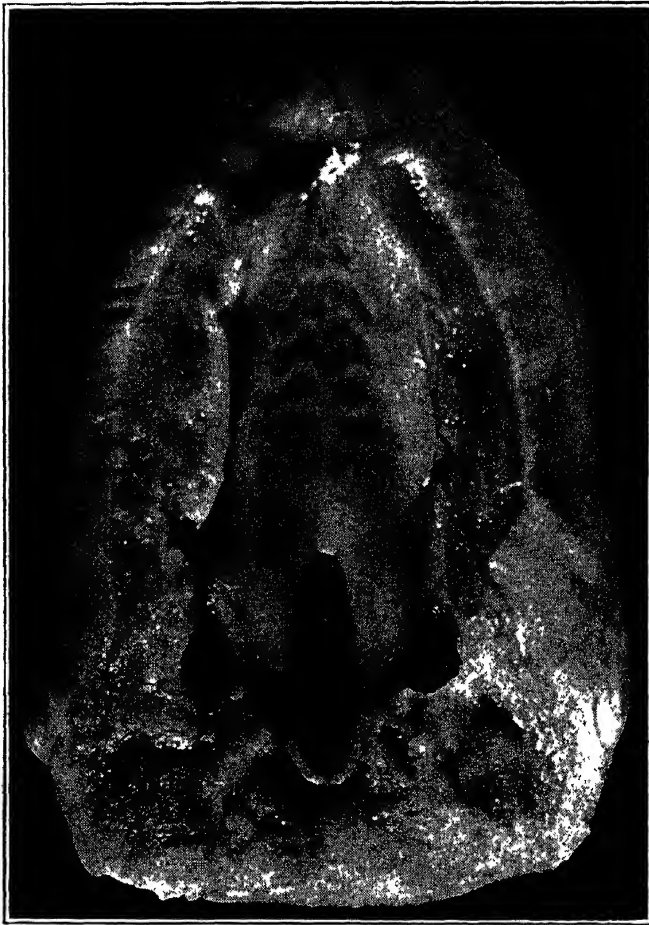


Fig. 16—Partial (posterior) cleft palate. (J. Warkany, R. C. Nelson, and E. Schraffenberger: *Am. J. Dis. Child.*)

27 were infants less than a year of age and two of these were one week of age. Since the two infants had been nursing their mothers, it seemed possible that they might have obtained the infection by way of the breast milk. Symptoms shown by the infants included fever, convulsions, bulging fontanel, and generalized muscular rigidity. The most strik-

later years. In some instances the diagnosis of equine encephalitis was not suspected until symptoms of mental retardation and spasticity developed with a history of an acute illness dating back to the summer months when the epidemic of encephalitis occurred.

The *antitoxin* of *Staphylococcus aureus* occurred in approximately the same

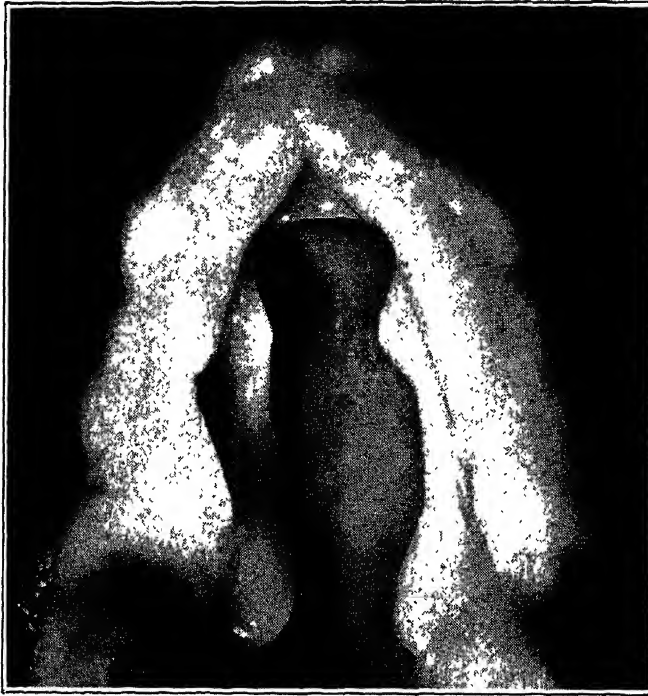


Fig. 17—Physiologic cleft palate in a rat fetus. (J. Warkany, R. C. Nelson, and E. Schraffenberger: *Am. J. Dis. Child.*)

titers in the blood of mothers and their offspring examined by J. A. Lichty, C. P. Katsampes, and W. S. Baum.<sup>72</sup> The anticapsular agglutinin was also studied and although its levels in mother and infant showed a positive correlation, the relationship was not as close as in the case of the antitoxin. The antitoxin titer in the different mothers varied consider-

ably, but that of each mother and her infant were closely correlated. Of the group of 50 infants, 30 had titers higher than their mothers, 18 had identical titers, and two had lower titers. The infants tended to lose the antitoxin from their blood during the first four months of life; those with high titers losing it more rapidly than those with low titers.

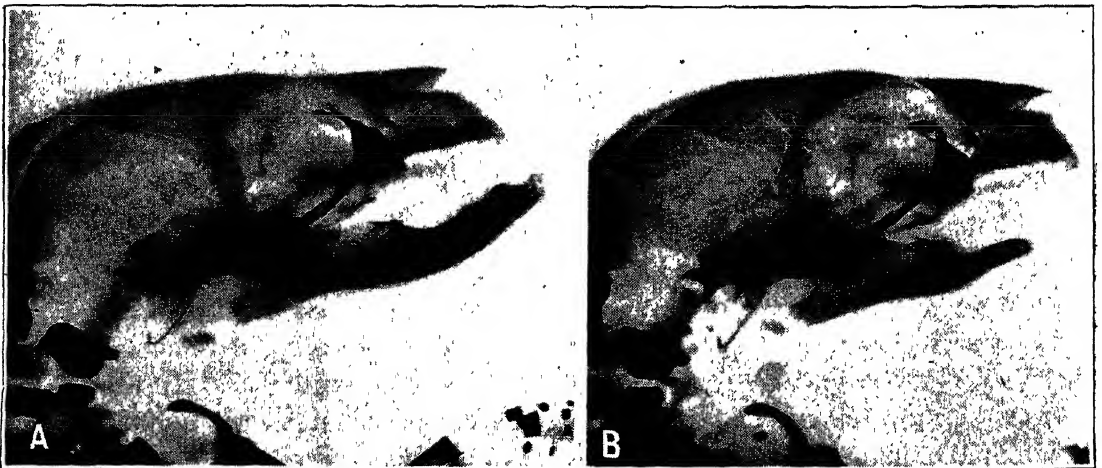


Fig. 18—*A*, Cleared head of normal newborn rat. *B*, Cleared head of abnormal newborn rat, showing micrognathia. (J. Warkany, R. C. Nelson, and E. Schraffenberger: *Am. J. Dis. Child.*)

The level of agglutinins remained fairly constant throughout the first year of life. The clinical significance of the protection offered the newborn infant by these substances has not yet been evaluated.

*Perforation* of the gastroenteric tract can occur at any site but the ileum is the most common. In a patient observed by H. A. Agerty, A. J. Ziserman, and C. L. Shollenberger<sup>73</sup> symptoms which developed two days after birth consisted of rapid respirations, loss of weight, poor color, and distention of the abdomen. Roentgenograms showed air in the abdominal cavity. At operation a small perforation in the ileum was repaired and the infant recovered. The cause of this condition in this patient was not determined but in other patients, etiologic factors in perforation of the digestive tract have been peptic ulcer of the stomach, infection, appendicitis, Meckel's diverticulitis, intussusception, trauma and anomalies of the enteric tract produced by atresias, bands, volvulus, and inspissation of meconium. Perforations have even occurred before the birth of the infant, and the cause in such cases is probably maternal infection. One of the most common of the above causes of perforation of the ileum has been the inspissation of meconium which may be the result of abnormal secretion of pancreatic juice caused frequently by cystic fibrosis of the pancreas.

### **Substances Transmitted from Mother to Infant**

Toxic reactions in the newborn due to sulfanilamide administered to the mother have been observed in two instances by A. M. Ginzler and C. Chesner.<sup>74</sup> One infant developed jaundice shortly after birth and had a large number of erythroblasts in the blood, but no anemia or enlargement of the spleen or liver. Sulfanilamide had been given to

the mother in large doses during the latter part of pregnancy; the level in the infant's blood, measured on the fifth day of life, was 1.5 mg. per cent. At autopsy the liver showed signs of acute yellow atrophy and there were areas of necrosis in the adrenals, spleen, and lungs. The second infant developed slight jaundice and there were erythroblasts in the blood smear, a moderate degree of anemia, and slight enlargement of the liver and spleen. Following transfusions the child made a complete recovery. The mother in this instance had also received large doses of sulfanilamide but the infant's blood had not been examined for the presence of the drug. The authors emphasized the fact that the sulfa drugs pass readily through the placenta and may stimulate hemolysis, especially in infants who were sensitive to the drug.

Cigarette smoking by the mother seemed to have little or no effect on lactation and upon the infant in the studies made by H. H. Perlman, A. M. Dannenberg, and N. Sokaloff.<sup>75</sup> Nicotine was excreted in the milk and in the urine of mothers who smoked cigarettes, the quantity being in direct proportion to the number of cigarettes smoked. No effects of smoking on lactation could be ascertained. Nursing was accomplished as readily by mothers who were heavy smokers as by those who smoked little or not at all. Nicotine in the milk did not seem to cause vomiting or diarrhea of the infants and did not impede the average gain in weight.

### **Normal Variations**

Changes in the size and shape of the thorax during the first week of life have been studied by J. L. Goodman.<sup>76</sup> In a series of 68 infants examined on the first, fourth, and eighth days of life the chest was greater in width than in depth. The thoracic size decreased during the first

half of the week and then during the latter half of the week the width remained stationary but the depth increased slightly, although the birth size was not regained until later.

Oxygen levels in 36 newly born infants, eight hours to 14 days of age, have been studied by C. A. Smith and E. Kaplan.<sup>77</sup> Samples of blood were obtained from the umbilical cord and from deep punctures of the heel. The average oxygen saturation of the arterial blood obtained from the cutaneous tissues was 93 per cent and this was only slightly lower than the average levels of 94.7 per cent obtained from 22 adults. During the first two days of life the oxygen levels of the newborn were slightly lower than those obtained in subsequent days. The roentgenograms taken of several infants showed various degrees of atelectasis and the oxygen saturation generally occurred in inverse proportion to the amount of atelectasis. Generally, however, the oxygen levels rose rapidly and during the first three hours of life approached adult values, which would indicate a rapid rerouting of fetal circulation into channels characteristic of extrauterine life. The oxygen saturation of the arterial cord blood rarely gave any indication of the time required for readjustment to take place. In a series of premature infants the oxygen saturation varied widely during the first three weeks of life and tended generally to be lower than the average of full-term infants.

Studies of excretion of bile pigments have been carried out by R. J. Tat, T. J. Greenwalt, and W. Dameshek.<sup>78</sup> In the newborn infant bilirubin, rather than urobilinogen, occurred in the stools. As the bilirubin levels declined the quantity of urobilinogen increased, until about the seventh month of life the bilirubin disappeared. It seemed probable that bac-

terial flora were responsible for the reduction of bilirubin to urobilinogen but diet influences the nature of the bacteria which produce this result. Carbohydrate diets which cause a predominance of fermentative processes inhibited the reduction, while protein diets which produced putrefactive action caused the reduction reaction. The values of bilirubin and urobilinogen in the stools were increased in hemolytic anemias, and these measurements were useful in observing the cause of such diseases.

In three infants with erythroblastosis foetalis such measurements were made by W. Dameshek, T. J. Greenwalt, and R. J. Tat,<sup>79</sup> and they concluded from the increased amounts of bilirubin and urobilinogen present that the disease should be classified as a severe type of hemolytic anemia.

### Prematurity

Although an infant is considered premature if his birth weight is less than 2500 Gm. (5½ pounds), sex and race differences in birth weight and racial differences in gestation period may influence the criteria. N. A. Anderson, E. W. Brown, and R. A. Lyon<sup>80</sup> noted in a group of more than 5000 infants that the average birth weight of males was slightly greater than that of females and the average weight of white infants was greater than that of Negro infants. The average gestation period of white infants was 5½ days longer than that of Negro infants. When mothers with any type of illness were excluded from the series and when those with underweight babies and with short gestation periods were also eliminated, the racial differences in gestation periods were evident in the remaining group. It seemed logical therefore to establish a lower limit of normal birth weight, possibly 2300 Gm. (5 lb.) for the Negro race.

Mortality rates of prematurely born infants have been reviewed by A. W. Diddle and E. D. Plass.<sup>81</sup> Among 861 premature infants weighing less than 2500 Gm. (5½ lb.) at birth the average death rate in the first month of life was 17.7 per cent. Stillbirths occurred in 19.2 per cent of the group. The smaller the infant, the higher were the mortality rates. Maternal disease, such as toxemia, placenta praevia, and premature separation of the placenta, seemed to lead to high infant death rates. The type of delivery did not affect the infant except when version and cesarean section were resorted to. The duration of labor had little effect on mortality. Molding of the head and damage to the fetus sometimes occurred in spite of short labor. The type of sedative and anesthesia bore little correlation to the mortality rates and seemed to play an unimportant rôle in production of asphyxia of the newborn. Among the causes of death of the infants who came to autopsy, intracranial hemorrhage ranked high, atelectasis was frequent, and next in order were congenital anomalies and pneumonia, but in a rather large number of cases no definite cause could be ascertained. The authors concluded that there was little to be done to prevent premature birth and death except the treatment of maternal syphilis at an early stage of pregnancy. The only hope of reducing mortality rates seemed to be in the improvement of postnatal care.

The premature mortality rate observed by L. Flax, E. L. Levert, and R. A. Strong<sup>82</sup> in the year 1937 was 85.3 per cent. During the succeeding years it declined until, in 1940, only 42.2 per cent of prematures died. Part of the success in lowering the rate seemed to be due to the institution of a separate premature nursery, and an increase in the size of the resident staff and nursing staffs car-

ing for these infants. The causes of death were corroborated in many instances by autopsy findings. In the infants weighing less than 1250 Gm. (2¾ lb.) at birth, atelectasis, intracranial hemorrhage, and prematurity itself were the most frequent causes of death. In the heavier infants, diarrhea, syphilis, bronchopneumonia were often encountered in addition to the above causes. The figures are given in detail in the accompanying charts and tables.

TABLE II  
STUDY OF PREMATURE MORTALITY IN 859 CASES

<i>Causes of Death in Babies 1501 to 2000 Gm. in Weight (37.6%)</i>	<i>Per- centage</i>	<i>Num- ber</i>
Bronchopneumonia.....	24.6	46
Diarrhea.....	17.6	33
Prematurity.....	15.9	30
Atelectasis.....	14.9	28
Cranial injury.....	10.1	19
Syphilis.....	3.2	6
Otitis media.....	2.1	4
Icterus gravis.....	1.6	3
Upper respiratory infection...	1.6	3
Adrenal apoplexy.....	1.6	2
Abscess of lung.....	0.5	1
Gastrointestinal anomaly....	0.5	1
Anencephalic monster.....	0.5	1
Pyonephrosis.....	0.5	1
Enlarged thymus.....	0.5	1
Otitis media, pneumonia, meningitis.....	0.5	1
Hydrocephalus.....	0.5	1
Septicemia.....	0.5	1
Peritonitis.....	0.5	1
Dermatitis exfoliativa.....	0.5	1
Aspiration pneumonia.....	0.5	1
Total.....	98.2	188*

\* Autopsies were performed on 126 cases.  
(L. Flax, E. L. Levert, and R. A. Strong: J. Pediat.)

The average values of urea clearance in prematurely born infants were lower than those of full-term infants in the series studied by H. H. Gordon, H. E. Harrison, and H. McNamara.<sup>83</sup> In both groups of patients, however, the clear-

TABLE III  
STUDY OF PREMATURE MORTALITY IN 859 CASES

<i>Causes of Death in Babies 2001 to 2500 Gm. in Weight (19.7%)</i>	<i>Per- centage</i>	<i>Num- ber</i>
Diarrhea . . . . .	24.4	23
Bronchopneumonia . . . . .	18.4	18
Prematurity . . . . .	15.3	15
Atelectasis . . . . .	15.3	13
Syphilis . . . . .	7.1	7
Cranial injury . . . . .	5.1	5
Otitis media . . . . .	4.1	4
Hemorrhagic disease of newborn . . . . .	2.0	2
Upper respiratory infection . .	2.0	2
Abscess of lung . . . . .	1.0	1
Cellulitis . . . . .	1.0	1
Spina bifida . . . . .	1.0	1
Cardiac hypertrophy . . . . .	1.0	1
Adrenal apoplexy . . . . .	1.0	1
Ulcerative enteritis . . . . .	1.0	1
Pyoderma and pulmonary infarct . . . . .	1.0	1
Aspiration asphyxia . . . . .	1.0	1
Total . . . . .	99.7	98*

\* Autopsies were performed in 60 cases.  
(L. Flax, E. L. Levert, and R. A. Strong: J. Pediat.)

ances were generally lower than in older infants and children. The decreased clearance did not seem to be related to the amount of urinary flow, but was probably due to defective glomerular filtration. The reason for this impaired function may have been the fewer glomeruli present in the premature kidney or the presence of columnar epithelium lining the glomeruli which possibly interfered with filtration, but there is no proof that this is the sole cause for the decreased clearance.

Creatine and creatinine excretion by premature infants observed by E. Marples<sup>84</sup> was about the same as that of full-term infants providing the protein intake was high. The average coefficient ranged from 5.09 in premature infants to 5.04 for full-term infants, in terms of

milligrams of creatinine nitrogen excreted per kilogram (2.2 lb.) of body weight per day. When premature infants received human milk and an average protein intake of 2.5 mg. ( $\frac{1}{25}$  gr.) of protein per kilogram (2.2 lb.) they excreted less creatinine. Little or no creatine was excreted in premature infants when the diet contained less than 3 Gm. (46 gr.) of protein per kilogram (2.2 lb.) of body weight. When the protein intake reached 5 Gm. (75 gr.) or more there was an increase in the amount of creatine excreted, which corresponded with the amounts excreted by the average full-term infants, namely, an average of 1.93 mg. ( $\frac{1}{30}$  gr.) per kilogram (2.2 lb.) per day. The amounts of creatine excreted varied considerably in both premature and in full-term infants, but generally the levels could be related directly to the nitrogen metabolism.

An index of the maturity of a fetus may be found in the glomerular development of the kidney according to the studies of E. L. Potter and S. T. Thierstein.<sup>85</sup> The histologic sections of the kidneys of 1000 newborn infants have been reviewed in respect to the stage of development of the glomeruli. Almost all of the fetuses which weighed more than 2500 Gm. ( $5\frac{1}{2}$  lb.) and measured more than 47 cm. ( $18\frac{1}{2}$  in.) in length had complete glomerular development. The formation of the glomeruli seemed to be complete when the infant reached a weight varying from 2100 Gm. ( $4\frac{1}{2}$  lb.) to 2500 Gm. ( $5\frac{1}{2}$  lb.) and measured from 46 to 49 cm. (18 to 19 in.) in length. There was a closer correlation between the stage of development of the glomeruli and the weight and length of the infant than there was between the glomerular development and the gestation period of the infant. In the ordinary full-term infant, therefore, the development of the kidney ceased about one

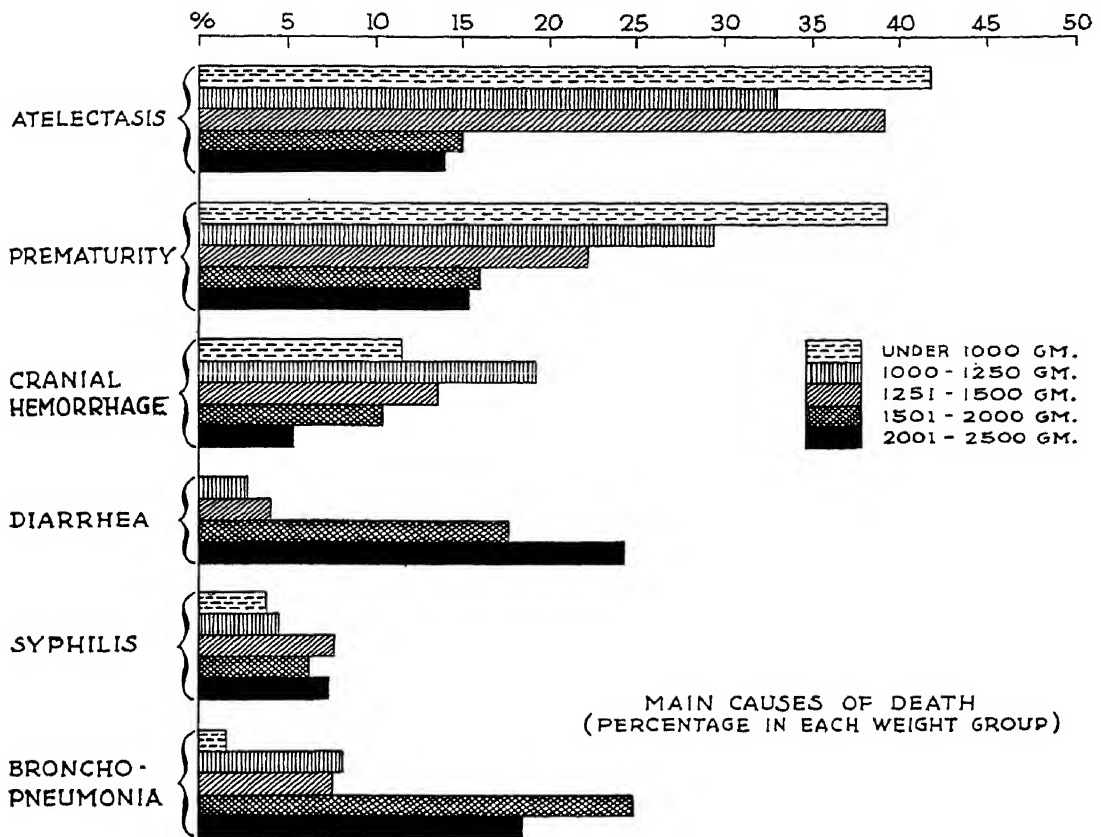


CHART 2

(L. Flax, E. L. Levert, and R. A. Strong: J. Pediat.)

month before delivery. Infants born after the thirty-fifth week of gestation had no immature glomeruli. Even though premature infants are born with underdeveloped kidney tissue the process of maturation probably continues after birth.

The relationship between the *icteric index* of the cord blood and the maturity of the infant has been investigated by B. Schick, S. B. Wiener, and M. Reiner.<sup>86</sup> In a group of 88 normal infants weighing between 2500 and 3840 Gm. ( $5\frac{1}{2}$  to  $8\frac{1}{2}$  lb.) at birth, the icteric index of the cord blood had an average value of 12.3 units; in 25 infants weighing more than 3840 Gm. ( $8\frac{1}{2}$  lb.) the average value was 11.8 units, and in 28 premature infants weighing less than 2500 Gm. ( $5\frac{1}{2}$  lb.) the average figure was 14.5 units. In each group, however, there were wide variations and after statistical analyses were made, no relation could be estab-

lished between the icteric index of cord blood and the maturity of the infant as judged by his weight, length, and sitting height at birth. The tendency, however, for the immature group of infants to have slightly larger amounts of bilirubin in the cord at birth would indicate that the placenta was actively engaged in breaking up hemoglobin before the birth of the infant and that this process was less active as the infant became more mature. Factors of blood volume, rate of blood formation and destruction, liver capacity, and other conditions probably cause the fluctuations in individual infants of all groups.

*Calcium and phosphorus requirements* of premature infants differed from those of full-term infants in the groups observed by H. R. Benjamin, H. H. Gordon, and E. Marples.<sup>87</sup> Three premature infants were fed human milk and



another three received cow's milk formulas for periods of three to 24 days and the calcium and phosphorus intake and excretion were measured. All received adequate amounts of vitamin D. The premature infant retained greater amounts of both minerals than full-term infants, and the amount of calcium and phosphorus available in human milk diets did not meet the requirements of the premature infant. Possibly the lack of sufficient amounts of phosphorus in the human milk influenced the inadequacy of calcium retention. On cow's milk diets the infants were able to retain amounts which would be sufficient to insure normal calcification of bony structure by the end of the first year of life.

Studies of *heat regulation* of premature infants have been conducted by R. Day, J. Curtis, and M. Kelly.<sup>88</sup> Among the physiologic factors which maintain normal body temperature are the rate of heat production and the rate of heat loss by radiation, conduction, and evaporation. A group of 25 premature infants were kept in a special calorimeter chamber and analysis was made of the heat and moisture lost during trial periods of 35 minutes. The effects of various atmospheric conditions on the rectal and skin temperatures of the infants were measured. In warm or cool air the vasomotor response of these infants was satisfactory and compared favorably with that of adults. In cool air the infants lost more than normal amounts of heat by radiation and conduction because of the large skin surface in relation to body weight. They also have a smaller amount of subcutaneous fat to act as insulation to conserve body heat. In such an atmosphere the infant increased the amount of his muscular activity and crying which increased the amount of heat produced. In warm atmospheres, the infants' temperatures rose to higher than normal

levels, possibly owing to inadequate sweat production, which usually facilitates heat loss.

### Tetany

Tetany in the newborn may be caused by disturbed kidney function as well as by low blood calcium levels. A series of 11 infants one day to six weeks of age who were observed by C. E. Snelling<sup>89</sup> had low serum calcium and elevated serum phosphorus levels. They improved clinically after the intravenous administration of calcium gluconate. These infants likewise had retention of nonprotein nitrogen and creatinine in the blood stream. In two instances, congenital malformations of the kidneys were found. In other patients the disturbed kidney function may have been due to insufficient fluid intake. It seemed probable that the inadequate secretory function had led to a hyperphosphatemia which affected the level of calcium in the blood.

### Vitamin K

The oral administration of synthetic vitamin K in oil to mothers at least four hours before delivery prevented low levels of prothrombin in the series of newborn observed by C. E. Snelling and W. Nelson.<sup>90</sup> Five capsules, each containing 1 mg. of the synthetic vitamin, were given to every other mother at the onset of labor, and the levels of prothrombin in their infants were observed daily for ten days. The infants of the control group of mothers had lower average levels than the infants of the treated group. The infants of the mothers who had no therapy tended to have lower average prothrombin levels in February and March than in January, April, or May. No correlation between these findings and the diets of the mothers could be determined.

Vitamin K may be absorbed readily through the skin, according to the experi-

ments of H. Vollmer, C. Abler, and H. S. Altman.<sup>91</sup> The synthetic vitamin was mixed with liquid petrolatum which had been thinned by the addition of odorless kerosene. About four drops of the liquid contained 1 mg. of the vitamin K. In this thinner medium the material was absorbed more rapidly than in heavier oils. From 0.1 to 1 mg. of the vitamin applied to the skin was effective in preventing the decline in prothrombin levels during the first few days of life. The speed with which the vitamin was absorbed was less rapid with cutaneous application than by oral administration but probably was more rapid than when it was given intramuscularly.

Low prothrombin levels were observed in mothers receiving barbiturate by J. E. Fitzgerald and A. Webster.<sup>92</sup> Even small amounts administered during labor reduced the prothrombin in the mothers and their newborn infants, but the levels could be restored by the administration of vitamin K.

The value of administration of vitamin K to mothers for the prevention of hemorrhage in the newborn infant has been questioned by J. Parks and L. K. Sweet.<sup>93</sup> They administered the vitamin orally to mothers before the delivery of their infants in 1151 instances and em-

ployed a series of 1594 untreated mothers as a control group. The only types of hemorrhage considered were melena, hematemesis, continued bleeding from the cord, gross subcutaneous hemorrhage, intracranial hemorrhage, or hemorrhage into other vital organs. Milder forms, such as vaginal bleeding, subconjunctival hemorrhage, cephalhematoma, and the vomiting of a small amount of brownish material, were eliminated from consideration. The incidence of gross hemorrhage in the group who received vitamin K was 1.7 per cent. In the group that received no vitamin K it was 1.4 per cent. Even in the underweight infants the incidence of hemorrhage was greater (4.5 per cent) when their mothers received the vitamins than in the control group (3.3 per cent). In the full-term infants, likewise, there was a greater incidence of hemorrhage in the treated than in the untreated group. Vitamin K did not prevent hemorrhage in infants delivered by cesarean section or by breech presentation. It was the conclusion of the authors that the vitamin K elevated the prothrombin levels in most mothers and infants but had no effect in the reduction of incidence of hemorrhage in the newborn infant.

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## NUTRITION

NORMAN KENDALL, M.D.

### Infant Feeding

The excretion of nicotine in the milk and urine of lactating women and the effect of cigarette smoking by the mother upon lactation and upon the nursing infant have been investigated by H. H. Perlman, A. M. Dannenberg, and N. Sokoloff.<sup>94</sup> A group of 55 women and their infants were studied. Nicotine was excreted in the milk and urine of all the

mothers who smoked cigarettes. There was a definite correlation between the quantity of nicotine excreted in the urine and milk and the number of cigarettes smoked; the quantity excreted in the urine was, in most instances, approximately ten times that in the milk. The smoking of cigarettes by the nursing women had no apparent effect upon lactation nor upon the nursing infants.



16B	Lima bean..... Dextrose..... Gelatin..... Oil..... Bone phosphate or dicalcium phosphate.....	32 35 15 18	19.1	18.8	56.1	3.2	3.1	9.3	1	5	3/4	2 3/4 7 1/4 5.0 4	4.0 7 1/4
17B	Dried peas..... Dextrose..... Gelatin..... Oil..... Bone phosphate or dicalcium phosphate.....	33 27 12 18	19.8	18.0	64.0	3.3	3.0	10.6	1	5.0		13 7 3/4 4.0 4.0	4.0 7 1/4
18	Soy flour..... Dextrose..... Oil..... Bone phosphate or dicalcium phosphate.....	46 42 12	18.0	20.0	54.9	3.0	3.3	9.1	1	5.0	1 1/2	8 1/4 2 1/4	3 1/4 5 3/4
19B	Rice flour..... Dextrose..... Gelatin..... Oil..... Bone phosphate or dicalcium phosphate.....	35 27 20 18	20.5	18.0	55.0	3.4	3.0	9.1	1	5		15 3/4 5 3/4 6 3/4 4	4 7
20A	Corn flour..... Dextrose..... Gelatin..... Oil..... Bone phosphate or dicalcium phosphate.....	40 26 16 18	19.8	18.7	56.2	3.0	3.1	9.3	1	5.0	1	1 1/2 5 1/4 5 3 3/4	4 1/4 7 1/2
	Cow's milk..... Human milk.....	100 100				3.3 1.4	4.8 3.7	4.8 7.4					

\* All percentages are by weight.

† All cereals are whole grain flours.

(L. Z. Wolpe and P. C. Silverstone: J. Pediatr.)

L. Z. Wolpe and P. C. Silverstone<sup>95</sup> have introduced a group of nine substitutes for milk for use in the treatment of milk allergy. The formulas consist of various types of flours, such as oat, barley, soy, lima bean, pea, taro, rice, rye, and corn, and such oils as cottonseed, olive, sesame, corn, peanut, and soy which were fortified with dextrose, gela-

The authors state that the preparations provide an adequate supply of the specific nutrients except for vitamins. The preparations are cheap, easily prepared, and their physical constitution resembles that of milk. These substitutes were used in a series of 20 patients with gratifying results and satisfactory developmental progress.

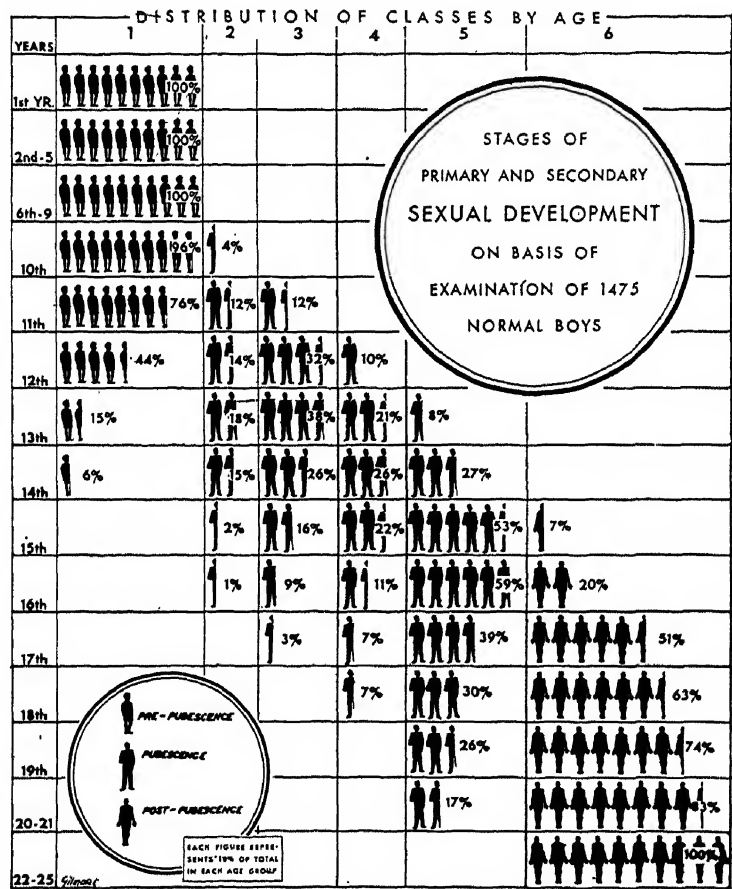


TABLE V  
AGE DISTRIBUTION OF THE VARIOUS STAGES OF PRIMARY AND SECONDARY SEXUAL DEVELOPMENT  
(W. A. Schonfeld: Am. J. Dis. Child.)

tin, vanilla, salt, saccharin, ferric chloride, and bone phosphate or dicalcium phosphate. The exact composition of the various substitutes are presented in the accompanying table.

The protein and fat content of the various preparations are approximately that of cow's milk, whereas the carbohydrate is two to three times that of cow's milk.

The use of cocoanut water in infant feeding was investigated by E. Soto Pradera, E. Fernandez, and O. Calderin.<sup>96</sup> Cocoanut water is a natural, sterile, and acid solution containing salts, proteins, carbohydrates, and neutral fats. In addition, it contains most of the necessary amino acids. A group of 31 normal infants were fed evaporated milk formulas containing cocoanut water as the

diluent. Satisfactory increase in weight was observed in all cases and no untoward effects were noticed.

The calcium and phosphorus requirements of premature infants were investigated by H. R. Benjamin, H. H. Gordon, and E. Marples.<sup>97</sup> Three premature infants were fed human milk and two

retention with a diet of human milk was inadequate to meet the requirements of the premature infant.

Growth and Development

In a discussion of male pubescence, W. A. Schonfeld<sup>98, 99</sup> presents criteria for the arbitrary division of development

	1	2	3	4	5	6
HAIRLINE						
FACIAL HAIR						
CHIN						
VOICE (Larynx)						
BREASTS						
AXILLARY HAIR						
BODY CONFIGURATION						
BODY HAIR						
PUBIC HAIR						
PENIS						
LENGTH (c.m.)	3-8.	4.5-9.	4.5-12.	8-15.	9-15.	10.5-18.
CIRCUMFERENCE (c.m.)	3-5.	4-6.	4-8.	4.5-10.	6-10.	6-10.5
TESTES (c.c.)	.3-1.5	1.75-6	1.75-8	2-20	6-20	8-25
PROSTATE	OR			S		S
	PRE-PUBESCENCE	PUBESCENCE			POST-PUBESCENCE	

TABLE VI  
STAGES OF SEXUAL DEVELOPMENT AND MATURATION  
(W. A. Schonfeld: Am. J. Dis. Child.)

cow's milk. Each infant received 20 drops of percomorph liver oil daily.

The premature infant was found to retain more calcium and phosphorus than full-term infants and the calcium of cow's milk was more fully retained than that of human milk. The authors believe that the poor utilization of calcium of human milk is on the basis of the low phosphorus content. In the opinion of the authors, the calcium and phosphorus

and maturation during pubescence into six stages on the basis of genital measurements and associated sex characteristics. (Table V, p. 566.) Fifteen hundred normal boys were classified.

In the second article the author describes the methods employed in measuring the genitals and presents charts and figures showing the growth of the penis and testes from birth to maturity. (Table VI, p. 567.)

The author draws attention to the great degree of variations of normal in the period of genital latency during prepubescence and in the age of onset of pubescence. The apparent hypogonadism in the obese boy is usually due to the fact that the penis is embedded in suprapubic fat. When the penis and testes of such cases are measured it is evident that they are within the range of normal. He states that the diagnosis of a Fröhlich type in these boys is unwarranted. The author proposes a test to determine whether a boy will have spontaneous pubescence. Five hundred to 700 I.U. of chorionic gonadotropin are injected three times a week for two or three weeks. If no response is observed, the dose is increased to 1500 I.U. three to five times a week for two or three weeks more. Evidence of response, manifested by enlargement of the penis, warrants the assumption that the boy has at least one normal testis and probably adequate anterior pituitary function so that he will have spontaneous pubescence. The test is also of value in differentiating bilateral cryptorchidism or delayed puberty from eunuchoidism.

C. C. Buehl and S. I. Pyle,<sup>100</sup> in a study of the skeletal age of children, have attempted to select the minimum number of the first appearance of ossification centers as an index of the total skeletal age. Thirty boys and 30 girls were included in the study. Additional data were obtained from a group of 100 girls. The authors found that the age of ossification of the distal epiphysis of the ulna, the first sesamoid of the thumb, and the crest of the ilium provided as reliable a measure of maturity as the concomitant mean total skeletal age in the group of children observed. The ages at which ossification began in each of these three centers correlated more closely with the menarcheal ages than did the corresponding mean

total skeletal age. Ossification began in the crest of the ilium within six months of menarche in two-thirds of the girls. The authors suggest that the onset of ossification in the crest of the ilium might possibly indicate a point in the maturation cycle of the male which is comparable to that existing in the female at the time of menarche.

In a further attempt to simplify the determination of bone age of children, L. A. Lurie, S. Levy, and M. L. Lurie<sup>101</sup> studied a series of 1129 children consisting of 704 boys and 425 girls ranging in age from  $2\frac{1}{2}$  to 19 years. Roentgenograms of the hand, including the wrist, the elbows, the pelvis, and the foot were taken of each child.

The authors present many charts representing the range of time of appearance and fusion of the epiphyses of the bones examined. The data are summarized in the accompanying figures which the authors claim may serve as a convenient guide for the determination of bone age in normal children. The authors conclude that the areas examined in this study are adequate for determination of the bone age of children. They advise against the use of the lesser trochanter because of the likelihood of distortions due to variations in focusing. In their series, as well as in those of others, girls exhibited a definite acceleration of bone growth as compared to boys. A new term, "bone quotient," which is obtained by dividing the bone age by the chronological age, is introduced. This figure is comparable to the intelligence quotient and is of value in furnishing a uniform basis for statistical studies.

### Obesity

I. P. Bronstein, L. J. Halpern, and A. W. Brown<sup>102</sup> studied a group of 46 obese children consisting of 28 females and 18 males. No evidence of glandular



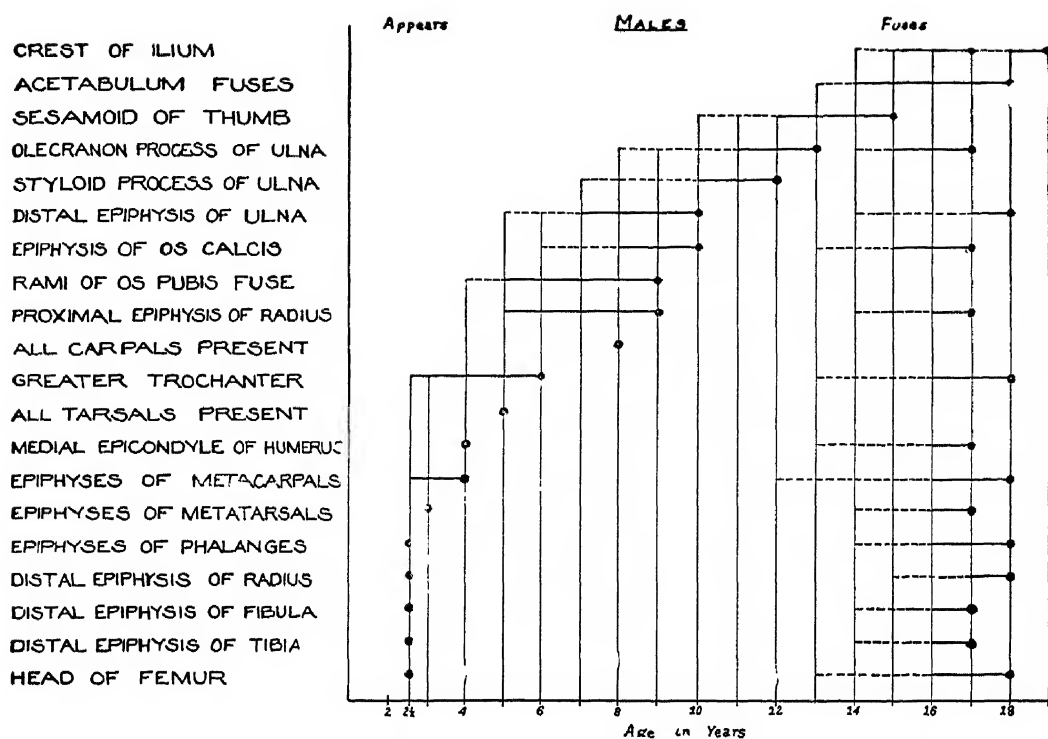


Fig. 19—Appearance and fusion of bone centers at various ages in boys.

(L. A. Lurie, S. Levy, and M. L. Lurie: J. Pediat.)

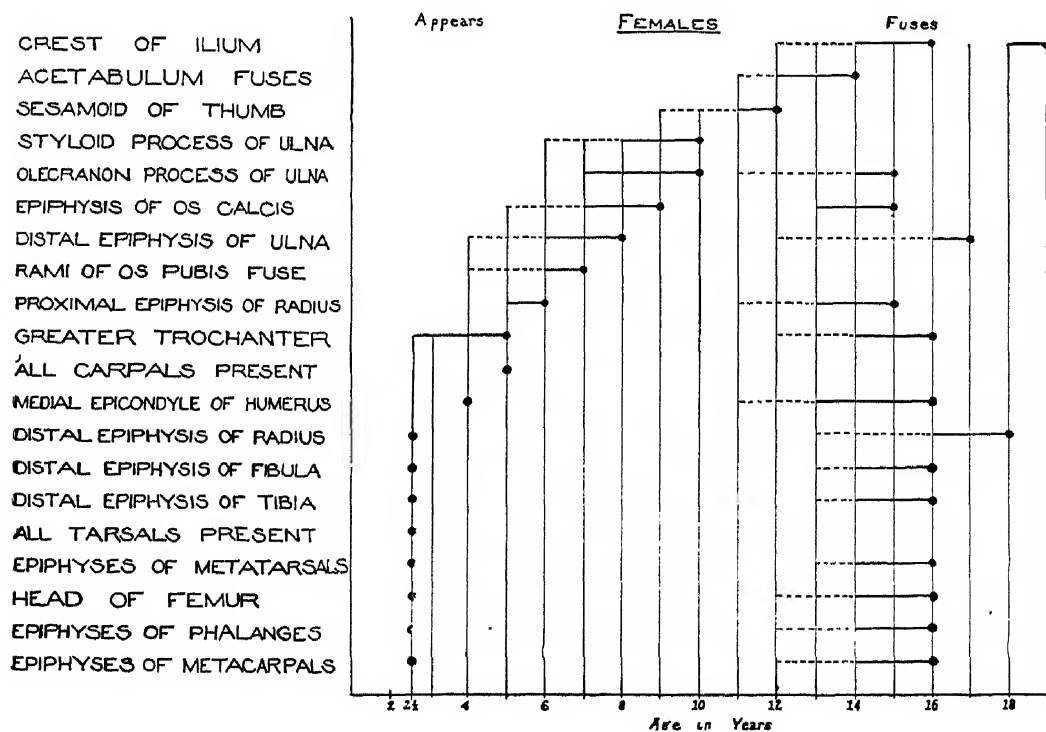


Fig. 20—Appearance and fusion of bone centers at various ages in girls.

(L. A. Lurie, S. Levy, and M. L. Lurie: J. Pediat.)

dysfunction as a possible basis for the obesity was found. Best results in reduction of weight were obtained by restriction of the caloric intake and fluids in the coöperative group. Endocrine therapy, consisting of *thyroid extract*, *chorionic gonadotropins*, and *whole anterior pituitary extract*, failed to produce any significant loss of weight. *Amphetamine sulfate* was administered to a small number of patients with questionable effect, as *dietary therapy* was simultaneously employed.

### Vitamin B<sub>1</sub>

The relationship of the blood level of vitamin B<sub>1</sub> to urinary thiamin was investigated by R. A. Benson, C. M. Witzberger, L. B. Slobody, and L. Lewis.<sup>103</sup> A group of 45 normal children consisting of 22 boys and 23 girls, ranging in age from 4 to 12 years, was studied. The blood level of thiamin was found to be between 4.8 to 12.3 micrograms per 100 cc., with a mean of  $7.8 \pm 1.3$ . The daily variations in blood vitamin B<sub>1</sub> in an individual child did not follow the daily urinary thiamin output. Although the daily urinary thiamin values varied considerably, the daily blood levels did not change accordingly. The blood level of thiamin was not proportional to the thiamin excreted or to the percentage of dietary thiamin which was excreted in the urine.

Further studies of the thiamin content of human milk were performed by E. M. Knott, S. C. Kleiger, and F. Torres-Bracamonte.<sup>104</sup> Employing the micro-fermentation method, 111 samples of milk from 50 women in all stages of lactation were analyzed. Colostrum was found to contain very little thiamin. As the period of lactation progressed, the thiamin values gradually increased and reached maximum values at approximately three weeks after parturition. The

average thiamin content of all samples was 15.1 µg. per 100 cc. of milk. The thiamin content of milk obtained from women who nursed their infants completely averaged 20.1 µg. per 100 cc., while that obtained from women who employed supplementary feedings for their infants averaged 9.3 µg. per 100 cc. of milk.

In subsequent studies, E. M. Knott, S. C. Kleiger, F. W. Schlutz, and G. Collins<sup>105</sup> have attempted to determine whether human milk feedings to young infants supplied adequate quantities of thiamin. Determinations of urinary thiamin were performed upon breast-fed and partially breast-fed infants. Urine specimens were collected for two consecutive four-hour periods. At the end of the first period some of the infants were given 100 µg. of thiamin per Kg. of body weight.

The urinary thiamin values were low for most of the infants who were breast-fed entirely and these values were not increased after the test dose of thiamin. Those infants who received formulas of evaporated milk in addition to breast feedings excreted larger amounts of thiamin in the urine. They also had significantly greater increases in the urinary thiamin values after a test dose of thiamin had been administered. The blood thiamin values for seven infants who were breast-fed entirely averaged 4.43 µg. per 100 cc., while those infants who received supplemental feedings of evaporated milk or whose mothers were given thiamin supplements averaged 5.83 µg. per 100 cc. of blood.

The authors conclude that young infants require approximately 200 µg. of thiamin daily, which necessitates that human milk contain 20 or more µg. of thiamin per 100 cc. in order to fulfill the infant's needs. They suggest that 40 µg. of thiamin per Kg. of body weight

may be a practical standard for the ordinary needs of the infant.

### Vitamin C

A study of the vitamin C content of the blood of children with scarlet fever, rheumatic fever, and diphtheria was carried out by A. F. Abt, L. M. Hardy, C. J. Farmer, and J. D. Maaske.<sup>106</sup> The average initial value of blood plasma ascorbic acid in patients with scarlet fever was 0.49 mg. per 100 cc., while that of a normal control group was 0.62 mg. per 100 cc. Of 76 patients observed, supplements of 300 to 600 mg. ascorbic acid were administered to 35 patients daily. The clinical courses of the two groups were similar. A group of 61 children with rheumatic fever and eight with acute pharyngeal diphtheria were studied. The initial blood ascorbic acid levels were not significantly different from those of the normal control group. A subgroup of the children studied were given supplements of vitamin C during the illness. Although the patients given the supplements did attain higher blood ascorbic acid levels, the course of the disease was unaffected.

The authors conclude that high temperatures *per se* do not significantly lower plasma ascorbic acid levels or increase to any extent its utilization in the body. Fever accompanied by active infection may increase vitamin C utilization.

### Vitamin D

The efficiency of a single dose of vitamin D for the prevention of rickets was studied by I. J. Wolf.<sup>107</sup> Seventy-five infants were given 600,000 U.S.P. units of an electrically activated preparation of ergosterol divided into two oral doses at about the third to the fifth month of life. The infants were maintained on diets devoid of antirachitic substances. Non-irradiated evaporated milk or a nonvita-

min D cow's milk was employed in the preparation of the formula. Of 43 infants examined roentgenologically at the onset of the study, 18 were found to have rickets.

The massive doses used in this study were well tolerated by the infants and no toxic manifestations were observed. The 18 cases of rickets observed at the onset of the study healed during the period of observation of two to seven months. Of the remainder of the group, 44 infants were observed for two to seven months after therapy and they failed to develop any evidence of rickets. The author suggests two plans for the prophylaxis of rickets:

1. The daily administration of 1000 U.S.P. units of vitamin D until the third month, at which time 600,000 units should be administered and repeated 4 or 5 months later.

2. The administration of 50,000 units of vitamin D at the end of the first and second months of life and 600,000 units at the third month. The massive dose of 600,000 units should be repeated 4 or 5 months later.

In a subsequent report, I. J. Wolf<sup>108</sup> cites the dangers of daily administration of large doses of vitamin D. To a male infant with a meningomyelocele, spina bifida, hydrocephalus, and palsy of the lower extremities, weighing  $7\frac{1}{2}$  pounds at one month of age, 300,000 U.S.P. units of vitamin D were administered daily for 14 days. Following a cisternal tap, the infant died suddenly. Microscopic sections of the kidneys showed calcification of the renal tubules. In this instance, toxic effects were produced by the daily administration of 85,000 U.S.P. units of vitamin D per Kg. of body weight for a period of two weeks.

Additional data supporting the view that massive doses of vitamin D therapy are effective and safe in rickets prophylaxis are presented by A. C. Rambar, L. M. Hardy, and W. L. Fishbein.<sup>109</sup> To a group of ten infants 600,000 U.S.P.

TABLE VII

PREVALENCE OF RICKETS ACCORDING TO AGE AND COLOR\*

Age Prevalence					Color Prevalence					
Age, Years	No. of Subjects	With Rickets	Without Rickets	Percentage with Rickets	White			Negro		
					No. of Subjects	With Rickets	Percentage	No. of Subjects	With Rickets	Percentage
2 to 3	67	38	29	57	22	13	60	45	25	55
3 to 4	36	18	18	50	18	9	50	18	9	50
4 to 5	29	11	18	38	10	2	20	19	10	53
5 to 6	19	8	11	42	5	2	40	14	6	43
6 to 7	15	5	10	33	6	1	16	9	4	44
7 to 8	14	6	8	43	8	6	70	6	0	0
8 to 9	15	7	8	47	6	4	66	9	3	33
9 to 10	9	2	7	22	6	0	0	3	2	66
10 to 11	8	5	3	62	3	1	33	5	4	80
11 to 12	9	4	5	44	6	3	50	3	1	33
12 to 13	5	2	3	40	3	1	33	2	1	50
13 to 14	4	1	3	25	2	0	0	2	1	50
	230	107	123	46.5	94	41	43.6	136	66	48.5

\* R. H. Follis, Jr., D. Jackson, M. M. Eliot, and E. A. Park: Am. J. Dis. Child.

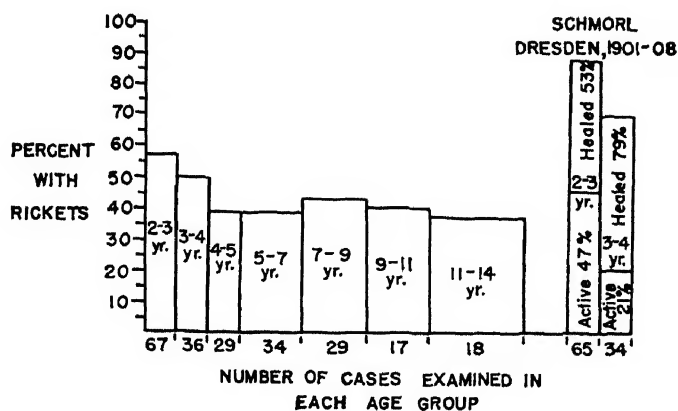


Fig. 21.—Graphic representation of the prevalence of rickets in the various age groups studied. Schmorl's results for the third and fourth years of life are added for comparison. (R. H. Follis, Jr., D. Jackson, M. M. Eliot, and E. A. Park: Am. J. Dis. Child.)

units of vitamin D were given orally in one dose; to another group of ten infants 100,000 U.S.P. units were given once each month for six months. Blood calcium and phosphorus levels and roentgenograms of the long bones were taken each month. None of the infants showed any evidence of toxicity nor any clinical or laboratory sign of rickets. In no in-

stance did the blood calcium level rise above the normal limit.

An interesting and important contribution on the incidence of rickets among children has been made by R. H. Follis, Jr., D. Jackson, M. M. Eliot, and E. A. Park.<sup>110</sup> The data are based on the postmortem examination of 230 children ranging in age from 2 to 14 years. The

diagnosis of rickets was made by histologic study of the bones. Roentgenograms of all bones removed at autopsy were taken.

Of the group studied, 107 or 46.5 per cent were found to have rickets (SEE: table and figure). The incidence in the white children was 43.6 per cent and 48.5 per cent in the Negro children. In 23 per cent of the total group the disease was classified as slight, in 18 per cent as moderate, and in 4.8 per cent as advanced. The incidence of rickets in children dying of acute illness was 67 per cent in contrast to 41 per cent in the group dying from chronic illness. Rickets was evident in the roentgenograms taken at autopsy in only six cases; in three of the 38 children between two and three years of age; in two of the 18 children between three and four years of age, and possibly in one of the 11 children between four and five years of age. In none of the children between the ages of five and 14 years was there any signs of rickets in the postmortem roentgenogram. The greatest prevalence of rickets was in the winter months, December to February; the lowest in the autumn months, September to November.

The authors state that the histologic method for detecting rickets is extremely delicate, and it did not seem unusual that rickets was recognized by roentgenograms in only six cases because the changes at the cartilage-shaft junction are apt to be confined to so narrow a stratum that they do not show clearly.

### Vitamin E

J. F. Pohl and D. Baethke<sup>111</sup> confirm the work of others that vitamin E is of no benefit in the treatment of progressive muscular dystrophy. *Wheat germ oil* was administered daily for a period of 5½ months. No improvement having occurred, the daily dose was increased to

approximately 30 teaspoonfuls. In addition, supplements of *thiamin* and *pyridoxine hydrochloride* were administered for an additional period of seven months. Of the 15 patients observed over a period of 22 months, none was objectively improved.

### Vitamin K

Sufficient data have been accumulated proving that the oral or parenteral administration of vitamin K prevents or lessens hypoprothrombinemia in newborn infants. H. Vollmer, C. Abler, and H. S. Altman<sup>112</sup> investigated the efficacy of the percutaneous route. The preparation employed contained *menadione* in 80 parts of liquid petrolatum and 20 parts of odorless kerosene, and it was administered percutaneously on the first day of life.

Doses of 1.0 and 0.1 mg. of menadione were equally effective in preventing hypoprothrombinemia during the neonatal period. Doses of 0.01 mg. were effective in some infants and ineffective in others. The medication is apparently absorbed from the skin within four hours. One infant suffering with hemorrhagic disease of the newborn was treated with 1 mg. of vitamin K administered percutaneously. Within four hours, the prothrombin time dropped from 240 to 120 seconds and all evidence of bleeding ceased.

In addition, the effect of percutaneous administration of 1 mg. of vitamin K to 15 women before delivery was investigated in relation to the prothrombin time of the infant. The infants of mothers who received the injection two to 15 hours before delivery failed to develop the physiologic hypoprothrombinemia.

The authors conclude that the percutaneous administration of vitamin K to the newborn infant is a safe, simple, and reliable procedure.

The prevention of hypoprothrombinaemia in newborn infants by the administration of vitamin K to women prior to delivery is a well-known fact. C. E. Snelling and W. Nelson<sup>113</sup> have attempted to determine how near delivery vitamin K could be given and still be effective. The oral administration of 5 mg. of vitamin K in oil to mothers at least more than four hours before de-

livery prevented extreme degrees of hypoprothrombinaemia in the infant during the first week of life. The prothrombin time of the cord blood of those infants whose mothers received vitamin K within four hours of delivery was prolonged, whereas none of those whose mothers received vitamin K more than four hours before delivery took place was prolonged.

## PARASITIC DISEASES

NINA A. ANDERSON, M.D.

From the results of their studies Z. Bercovitz, R. C. Page, and E. J. de Beer<sup>114</sup> conclude that *phenothiazine* is not an effective anthelmintic or amebicide in the patients studied and that it is capable of causing toxic reactions. In an experimental study with rats after 18 days of oral administration of the drug, autopsy revealed hypoplasia of all of the cellular elements of the bone marrow in one case and normoblastic hyperplasia of the bone marrow in another. Among 24 humans with chronic ulcerative colitis or lymphogranuloma venereum or intestinal infections with various helminths or protozoa, who received 1.3 Gm. (20 gr.) of the drug *t.i.d.* for ten days (40 Gm. [ $13\frac{1}{3}$  5]), three had a decrease in the erythrocyte count of more than 1,000,000; nine had a decrease in the hemoglobin concentration of more than 10 per cent; six had a trace of albumin in the urine; one had a marked albuminuria; two had cylindruria; one had hyaline and cellular casts in the urine; two had nausea and vomiting after 6 Gm. (90 gr.) and 18 Gm. (4.5 5), respectively, and one had nausea after 40 Gm. ( $13\frac{1}{3}$  5) of the drug. The urine was a brownish red color while the drug was taken. There were no significant changes in the white blood cells.

In the treatment of various types of intestinal parasitic infections, using a dosage of 0.6 Gm. (10 gr.) *b.i.d.* for ten days (13 Gm. [ $3\frac{1}{4}$  5]) for children two to six years of age, 0.6 Gm. (10 gr.) *t.i.d.* for ten days (20 Gm. [5 5]) for children six to 12 years of age, and 1.3 Gm. (20 gr.) *t.i.d.* for ten days (40 Gm. [ $13\frac{1}{3}$  5]) for adults, results shown in Table VIII were obtained.

### Pinworm Infestation

**Enterobiasis** — E. Kuitunen-Ekbaum<sup>115</sup> studied the incidence of enterobiasis among 300 children and 56 adults in Toronto homes and found that 60 per cent of the children and 52 per cent of the adults had pinworms. The highest incidence was in the age group six to 11 years, and there were more instances of infection among females than males. There was a familial incidence in 29 of 34 family groups studied. An average of 6 NIH swabs were examined for each patient.

E. C. Jones<sup>116</sup> examined 60 white and 60 Negro hospitalized children and found that 17, or 14 per cent, were infested with pinworms. Fifteen of these, or 88 per cent, were white children. The specimens were obtained on alternate days between 11 P. M. and 1 A. M., after the

TABLE VIII

Parasite	Stool Examination		
	Before Treatment	After Treatment	
	Number of Patients	Patients Positive	Patients Negative
<i>Enterobius vermicularis</i> .....	10	8	2
Hookworm.....	3	3	0
<i>Ascaris lumbricoides</i>	2	2	0
<i>Taenia saginata</i> ....	2	2*	0
<i>Schistosomum mansoni</i> .....	1	1	0
<i>Trichuris trichiura</i> ..	9	9	0
<i>Endamoeba histolytica</i> .....	3	2	1
<i>Endamoeba coli</i> .....	7	7	0
<i>Giardia lamblia</i> .....	3	3	0
<i>Iodamoeba buetschlii</i>	2	2	0
<i>Diendamoeba fragilis</i>	1	1	0
<i>Endolimax nana</i> ....	1	1	0
Totals.....	44	41	3

\* In one case, after treatment with *olcoresin* of *aspidium*, the scolex was obtained.

children had been asleep at least two hours, by the NIH swab technic. The average number of swabs per patient was 2.9.

A. H. Jacobs<sup>117</sup> used Scotch cellulose tape to obtain his specimens for a study of enterobiasis among 228 children, one to 15 years of age. A piece of Scotch cellulose tape, the length of a glass slide, was folded over the end of a tongue blade with the nonadhesive surface of the tape against the tongue blade, and the pinworms were picked up by the sticky surface of the tape from the perianal folds. The tape was then spread out on the glass slide, adhesive surface down, and examined directly under low power magnification without a cover slip. In the first examination 72, or 31.3 per cent, were positive; in the second exami-

nation two more instances were found, and in a third examination one more. Infestation was noted among siblings and parents. In the group 22.6 per cent had no symptoms. A vaginal discharge was noted in 27.5 per cent of the females. Other symptoms included "nervousness" among 49.4 per cent, abdominal pain 41.3 per cent, underweight 41.4 per cent, anorexia 38.6 per cent, disturbed sleep 38.6 per cent, pruritis ani 21.3 per cent, and enuresis 17.3 per cent.

**Oxyuriasis**—In an extensive study of oxyuriasis E. B. Cram<sup>118</sup> found that treatment with *gentian violet*, 10 mg. ( $\frac{10}{65}$  gr.) per day for each year of apparent age, divided into three doses per day, was effective. Contraindications to the use of gentian violet include concomitant infection with *Ascaris lumbricoides*, moderate to severe cardiac, hepatic, or renal disease, alcohol in the digestive system, and diseases of the gastrointestinal tract. *Tetrachlorethylene*, administered in dosage of 0.1 cc. (1.5 m.) for each year of apparent age, given in 30 cc. (fl.  $\frac{5}{16}$ ) of a saturated solution of *magnesium sulfate* plus 60 cc. (fl.  $\frac{5}{16}$ ) of water or in a suitable dose of a solution of *magnesium citrate*, had greater efficiency in effecting cures in persons lightly infected than in those with heavier infestations. *Hexylresorcinol* and *santonin* gave unsatisfactory results. A cure was established when seven consecutive daily NIH swabs, taken 10 to 42 days after the end of treatment, were negative. The swabs were taken immediately after the patient arose, before he bathed or went to the toilet. The author stresses the importance of investigating whole families for pinworm infestation. A dermal test prepared with an antigen from adult and larval forms of *E. vermicularis* in 1:100 dilution appears to have a high degree of specificity, but nonspecific reactions



are obtained with an intradermal test in dilutions up to 1:5,000.

### Giardiasis

P. B. Welch<sup>119</sup> has reported in 13 patients with giardiasis fluoroscopic and radiologic evidence of motor or inflammatory changes in the duodenum, the duodenal cap, the pylorus, or the prepyloric portion of the stomach, which showed improvement in seven of the ten who were reexamined after the administration of *atabrine*. There was an eosinophilia ranging from 4 to 11 per cent in seven of the patients, which dropped to normal in five instances following the treatment.

## POISONING IN CHILDREN

### Benzedrine

A. J. Hertzog, A. E. Karlstrom, and M. J. Bechtel<sup>120</sup> have reported the death of a 12 months old girl who developed cyanosis, apnea, a rapid and weak pulse, erythematous blotches, and coma from the accidental ingestion of about 40 mg. ( $\frac{2}{3}$  gr.) of *amphetamine sulfate*. The lung showed a mottled hemorrhagic color and generalized edema, the stomach was dark and hemorrhagic, and the adrenals were diffusely hemorrhagic. There is no specific antidote for this poison.

### Castor Bean

L. A. Koch and J. Caplan<sup>121</sup> have reported the illness of a seven year old child, two hours after ingestion of four castor beans. Forty-eight hours later, when admitted to the hospital, he was in stupor with cyanosis and tachycardia. His response to symptomatic treatment, which included the administration of 5 per cent *dextrose in physiologic solution of saline* intravenously, is shown by the chemical studies in Table IX.

A. E. Allin<sup>122</sup> has suggested the possibility of the use of an *antiserum* against the toxin, ricin, for specific therapy of this poisoning.

### Cyanide

Western choke cherry seed contains cyanophoric glucoside which breaks down into hydrogen cyanide in the gastrointestinal tract, producing hydrocyanide poisoning. The dried crushed seeds exposed to air apparently lose their toxic properties. M. Pijoan<sup>123</sup> has reported four cases, of which three recovered. Treatment included *gastric lavage* with weak solution of sodium bicarbonate, *enemas*, 15 per cent *magnesium sulfate* via a Levine tube into the duodenum, *lumbar puncture*, *intravenous dextrose solution* and *transfusions*.

### Food Poisoning

In a critical review of food contaminations and poisons G. M. Lyon<sup>124</sup> has pointed out pertinent data concerning food poisoning due to bacterial action and other forms of food intoxication.

### Lead

M. H. Matz<sup>125</sup> has reported the development of stippling, increased densities in the metaphyseal ends of the long bones suggestive of lead poisoning, and an episode of coma in a 20 months old white female with eczema, treated with plaster of lead oleate (Diachylon). There was no history of other lead ingestion. No significant amounts of lead were found in the urine and in the blood.

In a study of a large group of lead workers E. E. Evans, W. D. Norwood, R. A. Kehoe, and W. Machle<sup>126</sup> failed to find any beneficial effect from the daily oral administration of 100 mg. of *ascorbic acid* on the lead concentration of the blood or in the elimination of lead in the feces or in the urine. There was no difference in the physical condition of

TABLE IX

	<i>On Admission</i> <i>Mg. per 100 cc.</i>	<i>Second Day</i> <i>Mg. per 100 cc.</i>	<i>Third Day</i> <i>Mg. per 100 cc.</i>
Nonprotein nitrogen.....	100	68	40
Urea nitrogen.....	65	40	25
Carbon dioxide.....	43 (vol.)	53 (vol.)	50 (vol.)
Chlorides.....	455	512	513
Total protein.....	7.98 (Gm.)	6.95 (Gm.)	6.72 (Gm.)
Total base.....	147	147	

the men or in the number and the severity of complaints. There was no change in the erythrocytes or in the degree of stippling or in the hemoglobin. They concluded, therefore, that there was no reason to recommend the use of ascorbic acid to minimize the effects of lead absorption.

### Mercury

H. Gibel and B. Kramer<sup>127</sup> have reported instances of idiosyncrasy to 5 per cent *ammoniated mercury* and to *mercury bichloride solution*, 1:4000. A 22 months old white girl developed a generalized erythematous morbilliform rash and a temperature of 104° F., after 11 days of treatment with 5 per cent ammoniated mercury. There was albuminuria in the first urinalysis but none in subsequent specimens. A patch test with 5 per cent ammoniated mercury produced a reddened area after seven days, which remained red for 24 hours. A 14 months old white boy developed an eruption on the sixth day after wearing diapers which had been rinsed in a solution of mercury bichloride, 1:4000, before drying. There was urinary suppression with only three ounces on one day; otherwise the urinalyses were negative.

In general, the treatment consists in *removal of the mercurial*. In severe cases symptomatic treatment is indicated. The authors recommend that local ap-

plications be avoided if possible since ointment may macerate the skin. Moist *boric acid dressings* may be used to soften the crusts of dried serum. Secondary infections may be treated with *wet compresses* or *sulfathiazole ointment*. Bed clothes should be supported to prevent contact with the skin; the patient kept undressed, and on sterile sheets.

M. H. Bass<sup>128</sup> has reported the development of an eruption on the lips and on the face from contact with amalgam during a dental operation.

Immediate fatality followed the intravenous administration of 2 cc. (30 m.) of undiluted *mercupurin* in a 16 year old male with congenital heart disease who was being treated for peripheral edema. J. Vaughn<sup>129</sup> cautions against its use in seriously ill patients and suggests the possibility of idiosyncrasy with the fatality of an anaphylactic nature.

### Phenolphthalein

M. L. Blatt, F. Steigmann, and J. M. Dyniewicz<sup>130</sup> found no significant pathology, no instances of sensitivity or unfavorable reaction following overdosage of *phenolphthalein* to children. A child, 2½ years of age, received 0.75 Gm. (12 gr.); one two years of age, 1 Gm. (15 gr.); one three years of age, 8½ Gm. (130 gr.), and one 3½ years of age, 6½ Gm. (96 gr.) of phenolphthalein without significant urinary or stool find-

ings. They concluded that the laxative response to the drug bears little relationship to the child-adult weight ratio and that the action is due to the local stimulation and not to an effect following absorption. A fraction of the ingested phenolphthalein is absorbed and may be demonstrated in the blood stream and in the urine as a conjugate product for several days after its ingestion, but the cathartic action bears no direct relation to the amount so absorbed.

### Phosphorus

M. A. Brescia and J. M. Dobbins<sup>131</sup> point out that the absence of sugar in otherwise normal spinal fluid is pathognomonic of phosphorus poisoning. Phosphorus poisoning in children is due mainly to the ingestion of fireworks or of some form of rat or roach paste. They reported the case of a 16 months old infant who developed coma, gritting of the teeth, marked trismus, and opisthotonos from the ingestion of rat paste. Sugar was absent from the spinal fluid. Phosphorus was found in the vomitus by Sherer's test. The patient finally made an uneventful recovery. Recommended treatment includes *gastric lavage with potassium permanganate 1:500*, *10 per cent glucose in saline* intravenously, *calcium gluconate* intramuscularly, *magnesium sulfate* by mouth and a *high carbohydrate, low fat diet*.

### Sodium Fluoride

W. L. Lidbeck, I. B. Hill, and J. A. Beeman<sup>132</sup> point out the serious danger of sodium fluoride poisoning, as demonstrated in an instance where roach powder containing sodium fluoride was mistaken for powdered milk and 17 pounds added to ten gallons of scrambled eggs for hospital patients. Some rejected the food on account of the salty or soapy taste; others complained of numbness of the mouth. Early symptoms included nausea, vomiting, diarrhea, and abdominal pain. There was blood in the vomitus and in the stool. Collapse, characterized by pallor, weakness, thready pulse, shallow respirations, weak heart tones, wet cold skin, cyanosis, and dilated pupils, developed quickly and death occurred usually within two to four hours. Some of those whose course was longer developed urticaria, a mucoid nasal discharge, and paralysis of the muscles of deglutition, carpopedal spasm, and spasm of the extremities. At autopsy there were demonstrated edema, hyperemia, acute congestion of the viscera, and cardiac dilatation. In those instances in which death was delayed, there were petechial hemorrhages of the gastric and duodenal mucosa. Sodium fluoride was recovered from the scrambled eggs, the stomach contents, and samples of kidney and liver tissue.

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## POLIOMYELITIS

ROBERT A. LYON, M.D.

**Clinical Aspects**—An average incubation period of 12 days was noted in an epidemic of poliomyelitis observed by A. E. Casey.<sup>133</sup> From careful histories taken at the time, the incubation period was plotted from the day of exposure to the onset of the prodromal period.

There were variations of from five to 35 days with two peaks, the first at seven to nine days and the other at 14 to 15 days. The average was approximately 12 days. When the incubation period was figured from the time of exposure to the onset of paralysis there was a

more definite peak at approximately 17 days.

Second attacks of poliomyelitis occurred in four patients reported by N. B. Nelson and W. T. Green.<sup>134</sup> From their own observations and from the reports of others, the authors concluded that the average incidence of poliomyelitis was one or two patients per thousand population and that second attacks occurred in about one in every 1000 primary infections. The intervals between attacks in the four patients observed varied from two to eight years. Whether such patients lose their immunity or whether they incur infections of different strains of virus has not been proven.

**Mode of Infection**—The poliomyelitis virus penetrated the intestinal wall into sympathetic nerve fibers of a chimpanzee treated by H. A. Howe and D. Bodian.<sup>135</sup> The virus was introduced into the stomach by a tube and four days later the chimpanzee developed symptoms referable to the central nervous system. The animal was killed, and cultures which were made of the spleen and liver tissues were negative but examination of the celiac ganglia and right sympathetic chain showed changes characteristic of poliomyelitis. It seemed probable that the virus might reach the spinal cord by such a route.

The relationship between bulbar poliomyelitis and tonsillectomy has been explored by T. Francis, Jr., C. E. Krill, J. A. Toomey and W. N. Mack.<sup>136</sup> In one family five children developed bulbar poliomyelitis shortly after tonsillectomy and three of them died. Another sibling who did not have the operation failed to contract the disease but the virus was found in his stools. All of the persons who had been in contact with these children previous to operation were examined and virus was found in the stools of several children even though they

were many miles away from the patient when the poliomyelitis broke out. The method by which the virus was transmitted from one child to another was still obscure, but one conclusion emphasized by the authors was caution in advising tonsillectomy during the season when poliomyelitis might be prevalent because carriers of the virus might develop the disease.

*Pathologic changes* in cardiac muscle of seven patients who died of poliomyelitis were reported by A. R. Peale and P. F. Lucchesi.<sup>137</sup> On gross examination nothing was noted in the heart muscle except slight variations from the normal color and consistency. Microscopic examination showed degenerative changes with fragmentation of the fibers and edema and in five instances there were inflammatory reactions consisting of cellular infiltration. None of the patients had had clinical evidence of myocardial failure.

**Treatment**—The early treatment of poliomyelitis has been discussed in detail by J. A. Toomey.<sup>138</sup> So many different phases are covered by this review that one must resort to the article itself for any specific details. The author concluded, however, that there is *no specific medication* which has proved to be of any value. The sulfonamide drugs are contraindicated and there is no direct evidence that *blood serum* from convalescents is of any value unless, possibly, it is given in the preparalytic stage—and then it should be administered intramuscularly in repeated small doses. He was in hearty agreement with the excellent results obtained by the *Kenny treatment*, but questioned the method by which it accomplished its purposes. Any therapy which maintains a good blood supply and permits the few remaining fibers of the muscle to be kept in good condition would necessarily be

of value. The spasm of the opposing muscles did not seem to be so much of a problem as the possible degeneration of the few remaining fibers which are connected with the anterior horn cells. He disagrees with Sister Kenny in regard to *respirators* and believes that patients with paralysis of either the intercostal or diaphragmatic muscles should have the benefit of this type of treatment.

The application of *local heat* to a muscle which has apparently been paralyzed by poliomyelitis caused a temporary return of function in patients treated by J. A. Toomey.<sup>139</sup> The facial muscle was selected for observation and the heat was supplied by an infra-red lamp. Paralysis caused by poliomyelitis is often not complete because a few nerve cells remain intact in the central nervous system which are capable of supplying some of the muscle fibers. It was assumed that the application of heat to the muscle would restore the blood supply and serve as a stimulant to muscular action. In cases of peripheral neuritis all of the nerve fibers are destroyed and any treatment of the muscle would not produce cativity. The author compared the reaction of the facial muscle in three patients with poliomyelitis and in several others with peripheral nerve paralysis. In the latter cases no response followed the application of the deep infra-red therapy, but the patients with poliomyelitis tended to improve for a short time immediately after such treatment. The muscles in both types of patients also received passive stimulation with galvanic current and massage. It is probably impossible to differentiate between poliomyelitis and peripheral neuritis by means of this method alone because in both types of illness a few intact fibers remain which would always cause some contrac-

tion of the muscle. The therapy resembled the Kenny treatment, and the increase of blood supply to the local parts may be the factor which leads to improvement of function.

The results of various types of after-care of poliomyelitis patients has been reviewed by H. R. McCarroll.<sup>140</sup> In five groups of patients the amount of *physical therapy* and the *length of time of immobilization* of the impaired limbs differed but no significant differences in the results could be detected. In fact, the highest percentage of satisfactory results was obtained in the patients who received no treatment during early stages of the disease and began to walk without support as soon as possible after the acute illness. The differences in the rate and degree of recovery depended primarily upon the extent of the original paralysis. The author was unwilling to share the general enthusiasm for the Kenny treatment because it seemed to him that the lesions of poliomyelitis resided in the spinal cord and not in the peripheral nerves nor in the muscles. The local treatment of the latter structures would not seem to have any effect on the original pathological process.

*Vitamins B and E together with artificial fever therapy* have been tried in the treatment of patients with poliomyelitis by S. Stone.<sup>141</sup> Some of the patients were in the early stage of the disease, others were treated two to eight weeks after the onset and another group was treated as long as two months to two years after the acute attack. The artificial fever therapy was of some value in the reduction of the muscle tenderness and spasm. The vitamins seemed to aid regeneration and restoration of function of the muscles.

## RESPIRATORY SYSTEM

WALDO E. NELSON, M.D.

**Prophylaxis**

Considerable interest is being manifest in the control of *air-borne infection* in hospital wards and especially in the encouraging results obtained with *ultra-violet irradiation* and with *propylene glycol vapor*. Present data would indicate that both methods are effective in reducing the spread of air-borne infections. H. E. Sommer and J. Stokes, Jr.,<sup>142</sup> have shown not only that ultra-violet light is effective in reducing the number of air-borne organisms in a hospital ward but that an open connection between an irradiated and a non-irradiated ward had some effect in reducing the number of air-borne organisms in the non-irradiated ward. There was also a suggestive difference between the number of pneumococcal cross infections contracted in the irradiated and controlled wards in favor of the irradiated ones. In an experimental study, W. Henle, H. E. Sommer, and J. Stokes, Jr.,<sup>143</sup> have demonstrated that both ultraviolet irradiation and propylene glycol vaporation afford effective means for the control of air-borne infection in mice. There were significant differences between the number of infections and deaths of the control animals in contrast to those in the "treated groups." The data would indicate that under the limitations of these studies that propylene glycol vapor was somewhat more effective than ultraviolet radiation. They conclude, however, that both ultraviolet light and propylene glycol are effective disinfectants of the air and that their application depends upon the individual problem and the location to be disinfected. It is hoped that the method will soon be standardized for general use.

According to the data of D. W. Cowan, H. S. Diehl, and A. B. Baker,<sup>144</sup> *vitamins per se* have no effect in the prevention of the common cold. Their controlled study yielded no indication that either large doses of vitamin C alone or large doses of vitamins A, B<sub>1</sub>, B<sub>2</sub>, C, and D and nicotinic acid had any important effect on the number or severity of infections of the upper respiratory tract when administered to young adults who presumably were already on a reasonably adequate diet.

**Nose Drops**—The possibility of bacterial contamination of nose drops in dropper bottles is emphasized by the report of J. L. Gompertz and P. Michael.<sup>145</sup> When eight unused stock solutions of nose drops were cultured, no bacteria were isolated, but when the contents of 19 different dropper bottles which were known to have been used by one or more persons for at least one week were examined, all were found to have bacteria on culture. Apparently, repeated passage of the dropper from the nostril to solution had succeeded in each instance in establishing bacterial growth which was not controlled by the concentration of antiseptic in the solution. It is obvious from these observations that the use of the contents of contaminated dropper bottles by others, or in subsequent colds, is not without risk. Since sufficient antiseptic to insure sterility under circumstances of repeated contamination would make a solution unfit for intranasal use, the authors recommend that solutions which are to be used intranasally be prepared, sold, and used in such a manner as to avoid any contamination.

### Otitis Media

In an attempt to evaluate the efficacy of *chemotherapy* in the treatment of otitis media and especially in the treatment and prevention of mastoiditis, A. G. DeSanctis, V. de P. Larkin, and W. A. Gougelman<sup>146</sup> have analysed their data of recent years. A year by year breakdown of symptoms, physical signs, and laboratory data revealed that there has been no decrease in the severity of otitis media and mastoiditis in the last few years. A comparison, however, of the group of patients treated with *sulfonamides* against the group treated without sulfonamides from 1937 to 1941 shows an instance of mastoiditis of 9 per cent in the former and 30 per cent in the latter. It is their opinion that the one responsible agent for the reduction in the incidence of mastoiditis is chemotherapy. They have a strong preference for *sulfathiazole* rather than for *sulfadiazine*. They recommend a dosage of 0.065 Gm. (1 gr.) per pound of body weight per day in six divided doses.

### Tonsillitis

Good results in the treatment of tonsillitis, pharyngitis, and gingivostomatitis with the *bismuth salt of heptadiene-carboxylic acid in cocoa butter suppositories* have been reported by S. Silber.<sup>147</sup> It is said that subjective symptoms disappeared within 24 to 48 hours after treatment was begun and temperature dropped within 24 hours and was gone in from 36 to 48 hours in most cases. Signs of local improvement appeared within 24 hours. In patients in whom attacks of a similar nature had occurred, the duration of the earlier illness had been much longer in the same individual when treated otherwise than with bismuth. In only one patient were more than two suppositories required at 24 intervals. There were no local ill ef-

fects from the use of the suppositories and there were no toxic reactions to bismuth. It must be remembered, of course, that the conditions treated are, in the main, self limited and that adequate evaluation is difficult.

### Laryngeal Stridor

The lack of relationship between thymic disturbances and congenital laryngeal stridor is emphasized by R. H. Trimby.<sup>148</sup>

Congenital laryngeal stridor, the most common form of stridor in infancy, must be differentiated from other congenital abnormalities which interfere with respiration, such as a small glottic lumen, congenital web below the glottis, micrognathia, macroglossia, laryngeal papilloma, and cysts. Laryngeal spasm, perilaryngeal abscess, mediastinal tumor, foreign body and, at times, acute infections are important considerations. However, congenital laryngeal stridor has been most frequently confused with thymic disease, but simple thymic enlargement is rarely responsible for respiratory embarrassment in infancy. The pathology in congenital laryngeal stridor lies in an exaggeration of the infantile type of larynx with undue relaxation of the supraglottic structures. An accurate diagnosis can be made by direct laryngoscopy. The roentgen ray is a valuable aid in the study of these patients but *roentgen therapy* is without avail. Since this condition is usually outgrown, active therapy is seldom required.

### *Haemophilus Influenzae* Infections

Four cases of *Haemophilus influenzae*, type b, laryngitis with bacteremia are reported by P. G. du Bois and C. A. Aldrich.<sup>149</sup> In 1941 Sinclair first described this syndrome which is characterized by: (1) acute onset; (2) extreme prostration or "shock" out of all proportion



to local observations; (3) laryngitis of severe degree with marked edema and hyperemia of both the false and true vocal cords; (4) fever and neutrophilic leukocytosis of marked degree; (5) positive throat culture and bacteremia with *H. influenzae*, type b. In the authors' cases recovery was rapid and dramatic following **tracheotomy** and adequate **sulfonamide therapy**. The other child who did not have a tracheotomy had a much more prolonged course which was complicated. This condition occurs most frequently in pre-school children.

In a review of her experience in the treatment of *Haemophilus influenzae* infections, H. E. Alexander<sup>150</sup> states that the ideal treatment combines **specific antibody** with **sulfadiazine**.

In the case of the syndrome of pneumonia, empyema, and bacteremia in infants under one year of age, it is suggested that, in addition to treatment with sulfadiazine, 50 mg. of **antibody nitrogen** be given by intravenous injection and that its sufficiency be checked within a few hours by examining the patient's serum for excess of free antibodies by the capsular swelling method. Since meningitis is a frequent complication in these cases, it is suggested that a spinal puncture be performed, and if there is meningitis that it be treated appropriately.

In the case of acute obstructive respiratory infections which are frequently designated as acute laryngotracheobronchitis which are due to *H. influenzae*, the recommended treatment consists of **sulfadiazine** and **serum** with **tracheotomy** performed without too much delay when the indications merit it. Initially, sulfadiazine is administered intravenously and after 24 hours or so it is administered orally. In the attempt to estimate the severity of the disease and hence the need for the administration of antibodies it is suggested that an ap-

praisal may be obtained from a crude estimate of the concentration of type-specific carbohydrate present in the patient's serum. To patients who show a positive precipitin reaction within ten minutes after the test is set up, it is her custom to give an amount of type b. *H. influenzae* rabbit antibody which contains 50 mg. of antibody nitrogen. The adequacy of the dose is checked by examining the patient's serum for excess of free antibody by the capsular swelling method.

### Tracheotomy

The procedure of tracheotomy is generally considered to be a minor operation and one not likely to have serious complications. That this is not invariably so is pointed out by G. B. Forbes and G. W. Salmon.<sup>151</sup> They have observed 16 instances of mediastinal emphysema or of pneumothorax or of both following tracheotomy for some acute obstructive lesion. Not all of the children had symptoms attributable to these complications and the diagnosis in some instances was an incidental one made only from the roentgenogram. In eight of the children, however, there was marked respiratory distress and in six instances it was felt that the complication was either the immediate cause of death or was definitely contributory. In two of the fatal cases there was unilateral tension pneumothorax. It is emphasized that these complications may be sudden and unanticipated and may occur during tracheotomy or shortly thereafter. They advise immediate, careful examination of the chest, preferably by fluoroscopy, in all posttracheotomy cases in infants who exhibit circulatory or respiratory embarrassment. When pneumothorax occurs, aspiration of the air should be performed at once. In the less severe cases the air disappears spontaneously in from two to fifteen days, and it is suggested that

many instances of posttracheotomy mediastinal emphysema and probably some of pneumothorax remain unrecognized for lack of definite symptoms.

### Sulfonamides

The safety and effectiveness of the subcutaneous administration of *sodium sulfadiazine* has been demonstrated in infants by G. M. Jorgensen and D. McL. Greeley.<sup>152</sup> They have observed no evidence of injury to the tissues at the site of injection when five per cent solution of sodium sulfadiazine in distilled water was injected subcutaneously. The blood sulfadiazine levels after a single dose of five per cent solution of sodium sulfadiazine are shown in the table. Each of these infants received 0.1 Gm. (2 gr.) of sodium sulfadiazine per Kg. of body weight ( $\frac{3}{4}$  gr.) per pound). This mode of administration is an important one in the case of very sick infants who can-

not or will not take medication orally and in whom repeated intravenous administration is mechanically difficult.

### Expectorant

Some recent and important observations on the influence of expectorants and gases on sputum and the mucous membranes of the tracheobronchial tree have been made by Holinger, Basch, and Poncher. The summary of their article is as follows:

"A certain rationalization of therapeutic procedures used in the management of bronchopulmonary suppurations and obstructions may be suggested to coincide with the bronchoscopic observations and a study of the effect of therapeutic agents on sputum.

"In general, it may be stated that factors responsible for liquefying sputum within the bronchi, thus aiding in its evacuation, consist of those agents which

TABLE X  
SUBCUTANEOUS ADMINISTRATION OF SODIUM SULFADIAZINE

Case	Body Weight (Gm.)	Dose (cc.)	Blood Sulfadiazine Levels in Milligrams per 100 cc.				
			1 Hr.	2 Hr.	4 Hr.	6 Hr.	12 Hr.
1	2,730	5.5	14.0	15.0	14.0	11.0	8.3
2	3,110	6.2	13.0	12.0	11.0	9.0	5.1
3	3,420	6.8	16.0	15.0	13.0	12.0	9.9
4	3,770	7.5	15.0	15.0	13.0	11.0	8.3
5	3,940	7.9	14.0	15.0	13.0	11.0	8.2
6	4,640	9.3	15.0	13.0	13.0	11.0	8.0
7	6,350	12.7	15.0	15.0	12.0	8.6	3.2
8	7,120	14.2	15.0	14.0	12.0	9.0	5.0
9	7,500	15.0	14.0	15.0	12.0	9.9	6.2
10	8,190	16.3	17.0	16.0	13.0	9.1	5.3
11	10,700	21.0	15.0	18.0	17.0	13.0	8.5
12	11,300	23.0	17.0	15.0	12.0	9.5	5.1
13	11,600	23.0	14.0	15.0	14.0	10.0	4.9
14	13,100	26.0	14.0	12.0	9.0	6.2	3.2
15	16,500	33.0	15.0	17.0	15.0	13.0	7.6
16	16,600	33.0	15.0	16.0	16.0	14.0	8.7

Blood sulfadiazine levels after a single dose of 5 per cent solution of sodium sulfadiazine in distilled water, administered subcutaneously. Each patient received 0.1 Gm. of sodium sulfathiazole per Kg. of body weight ( $\frac{3}{4}$  gr. per lb.) (G. M. Jorgensen and D. M. Greeley: J. Pediat.)

will increase the hyperemia of the mucosa, as well as those which will increase the rate and depth of respiration.

"The action of the *expectorant drugs* is almost uniformly favorable in liquefying a portion of the sputum which lies in the first and second division bronchi but rarely affects the dependent viscid secretions in the peripheral bronchi.

"The actions of gas inhalations are quite specific, and they grossly influence the physical and chemical qualities of both the expectorated and the bronchoscopically obtainable sputum as well as the character of the bronchial mucosa. *Steam inhalation*, or the inhalation of a high humidity atmosphere, results in the liquefaction of sputum. *Carbon dioxide* has an action quite similar to that of steam, but to a greater degree. And, in addition, it increases the resorbing power of the bronchial mucosa; consequently it may be considered an extremely efficient expectorant.

"*Oxygen* acts very specifically as an antiexpectorant and, therefore, its use alone is contraindicated in obstructive lesions whose obstruction is in part, at least, due to copious, viscid secretions. This deleterious effect may be neutralized partially or wholly through the addition of steam and five to ten per cent carbon dioxide. In this manner not only the tremendous value of oxygen in alleviating the symptoms of respiratory embarrassment or even respiratory decompensation is retained, but also necessary aid in removing the obstruction is administered.

"The use of *codeine* and *atropine* at regular intervals over long periods of time is contraindicated in bronchopulmonary suppuration producing obstructive symptoms; however, the use of atropine prior to bronchoscopy may be justified in reducing the total amount of

secretion and thus making the procedure easier for the patient.

"Specifically, the use of the various agents described may be of distinct advantage in the treatment of certain diseases in manners determined through these studies. In bronchiectasis and in certain types of asthma in which bronchial obstruction plays a rôle in the symptomatology and pathology, frequent inhalations of carbon dioxide by mask, together with steam inhalations, may be used to augment the *postural drainage* and *bronchoscopic aspiration* which are fundamentally important. The use of steam and carbon dioxide between bronchoscopies, and especially shortly prior to bronchoscopy, is indicated if the sputum is known to be extremely thick and tenacious. Such therapy greatly enhances the action of any expectorant drug which is being administered.

"In laryngotracheobronchitis, the use of a room kept at 70° to 75° F. with a relative humidity of 80 to 95 per cent provides satisfactory conditions for liquefying secretions. If, because of an increasing edema, obstruction of the airway progresses in spite of the removal of secretions, oxygen may become necessary. In such instances adequate provision for a high degree of humidity in the oxygen tent is essential. The attachment of a mechanical humidifier to the tent in the manner suggested by Davison is the most practical means of accomplishing this.

"Postoperative massive collapse of the lung, produced by the occlusion of a major bronchus by viscid mucus, is almost always spontaneously relieved if the patient can be encouraged to breathe deeply and cough. Steam inhalations aid in liquefying secretions and thus facilitate their removal, but carbon dioxide has become the most commonly used expectorant in the treatment of this dis-

ase because of its extremely efficient action in increasing the rate and depth of respiration as well as in aiding to liquefy the secretions. Actual *bronchoscopic suction*, when these agents fail or if the condition of the patient demands immediate intervention, must always be available.

"The influence of the agents studied on the mucosa and inflammatory products of the nasal accessory sinuses has not been studied in detail. It remains to be seen whether an inflamed mucous membrane of the upper respiratory tract is similarly responsive to carbon dioxide when this action is not dependent on an actual increase in the respiratory movements."

### Sudden Death

Sudden death in apparently healthy infants is so frequently unexplained that it constitutes a real pediatric problem. J. M. Adams<sup>153</sup> has reported the clinical and postmortem findings in three infants dying suddenly without previous evidence of illness. The only significant pathologic change noted was a marked interstitial mononuclear pneumonia associated with diffuse pulmonary hemorrhages and edema. The author feels that pneumonia is probably the most important single cause of sudden death in infancy. In the cases reported it was felt that the absence of bacteria and the almost complete lack of a polymorphonuclear leukocyte response was in favor of a virus etiology.

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### SCARLET FEVER

ROBERT A. LYON, M.D.

A diagnostic test for scarlet fever which is the reverse of the Schultz-Charlton test has been suggested by J. D. Goldberg and J. De Hoff.<sup>154</sup> Blood serum was obtained from patients with doubtful scarlet fever on admission to the hospital and on the fourteenth and twenty-first day of the disease. These samples of the sera were injected intradermally into patients with definite scarlet fever rashes. Blanching never occurred with the first serum sample of a patient with true scarlet fever but did occur with the second specimen collected on the second or third week of the illness. Serum from patients not having scarlet fever caused either a consistent blanch or no blanching at all with the two specimens of serum.

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### SMALLPOX

The lowest incidence of smallpox for many years occurred in 1941, which is

the last year for which statistics are available. Fourteen hundred and thirty-two cases occurred in the entire country during that year, which was slightly more than half of the number that had occurred in 1940.<sup>1</sup> The highest incidence occurred in the northwestern states of Montana, Washington, Idaho, and Oregon. The lowest incidence occurred in the New England and the states on the eastern seaboard and southeastern part of the country. Indiana had an unusually high incidence rate. During the past 20 years more than a half million cases of smallpox have been reported in the entire country. In this period of time Indiana accounted for almost 38,000, possibly due to the low incidence of vaccination of school children in that state. Although the record of the past year is good, whether it indicates a definite downward trend, or only a temporary decline, is still questionable.

In the *treatment* of severe oriental smallpox with *sulfanilamide* the symptoms of the toxic stages were not relieved but the drug seemed to have a favorable effect on the complications and on the skin lesions, according to the observations of P. B. Wilkinson.<sup>155</sup> A series of 103 patients treated during a severe epidemic in Hongkong were included in the study. Of a group of 83 toxic patients first seen on about the fourth day of the disease only two survived and the administration of sulfanilamide seemed to have little or no

ence on the succeeding secondary skin eruptions and septic complications.

**Complications of Vaccination** — Various types of skin lesions occurring after smallpox vaccination have been noted by E. Bloch.<sup>156</sup> During an extensive campaign of vaccination in which about 500,000 persons were treated, 123 patients were known to have rashes but there may have been more. Most of these were of the urticarial or erythematous types, the latter resembling the exanthem of measles. They occurred most frequently in the children under 15 years

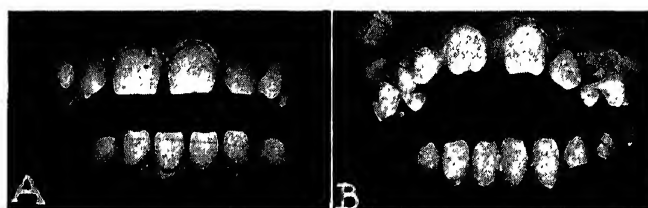


Fig. 22—Intraoral photographs of patients with congenital syphilis and Hutchinson incisors. *A*, Note in the upper central incisors the convergence of the proximal surfaces, the slight notch on the incisal edge and the diastema. This is the so-called screwdriver type. In the lower incisors, in addition to a convergence of the proximal surfaces, the notch on the incisal edge is more apparent (see Fig. 23 *A*). *B*, Note in the upper central incisors the convergence of the proximal surfaces in the incisal third of the crown, the distinct notch on the incisal edge and the diastema. In the lower incisors, the convergence of the proximal surfaces is apparent; the notch on the incisal edge is not pronounced (see Fig. 24 *B*). (B. G. Sarnat and N. G. Shaw: *Am. J. Dis. Child.*)

effect on the course of the illness. Forty-nine unvaccinated patients received the drug and in 19 of these the evolution of the skin lesions was halted at the papular stage, and the face and body were left covered with small, horny pox. In a group of 41 patients who had been vaccinated previously but who developed smallpox, the complications of boils, abscesses of the muscles and skin, otitis media, arthritis, and symptoms of the genitourinary tract, all improved or were prevented by the administration of sulfanilamide. It was the conclusion of the author that the drug had no effect on the virus itself and did not alter the course of the disease during the first few days when the toxic symptoms were manifest but exerted a favorable influ-

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## CONGENITAL SYPHILIS

**Diagnosis**—The incidence and nature of dental defects occurring in children with congenital syphilis have been re-

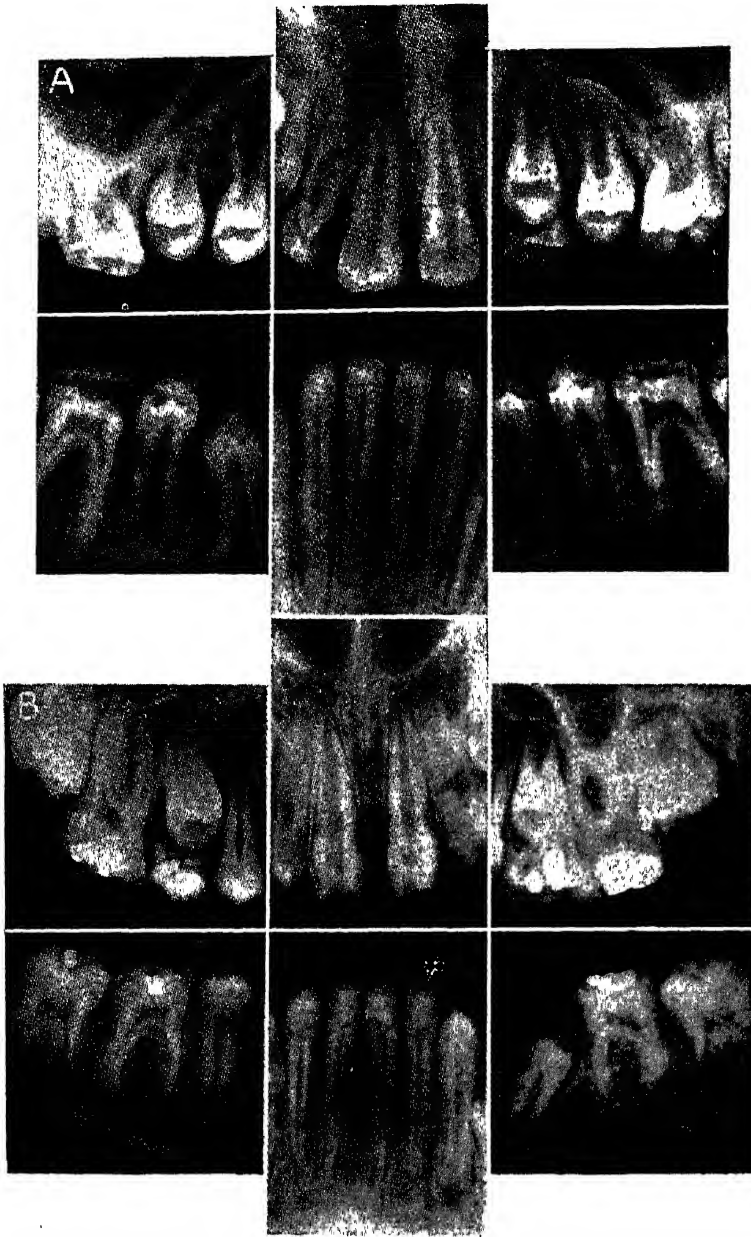


Fig. 23—Intraoral roentgenograms of the incisor and molar areas of the same patients with congenital syphilis described in Fig. 22. Note the size and shape of some of the permanent incisors (except the upper lateral incisors) and the permanent first molars (see Fig. 22). (B. G. Sarnat and N. G. Shaw: *Am. J. Dis. Child.*)

viewed by B. G. Sarnat and N. G. Shaw.<sup>157</sup> Among 57 syphilitic children above the age of seven years, 18 or 32 per cent had malformations of the teeth characteristic of syphilis. In 25 per cent of 16 younger children who still had deciduous teeth, roentgenograms of the permanent unerupted teeth showed malformations of a syphilitic nature. The

deciduous teeth of these patients were poorly enameled but there were no malformations. The characteristic change in the permanent teeth was the convergence of the lateral borders which occurred most often in the incisors and occasionally in the first molars. The notch incisors in the incisal border occurred in 14 instances. Defects in the enamel of

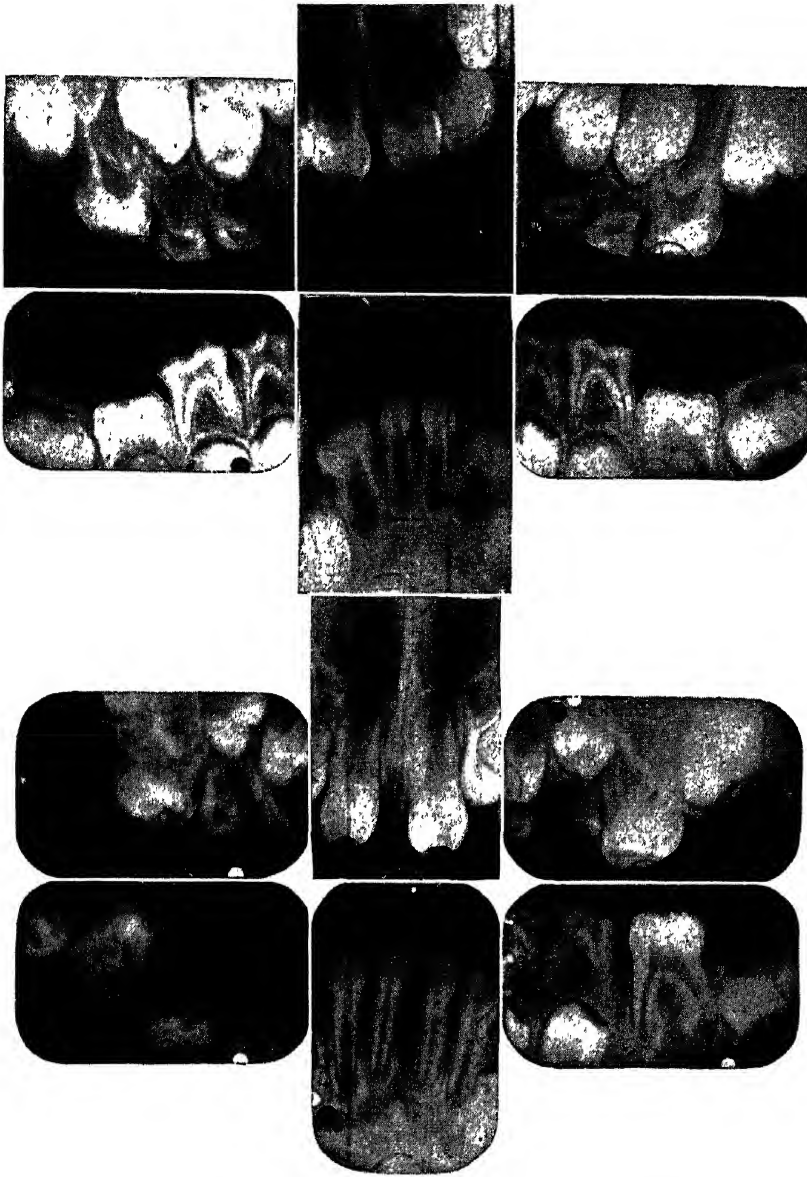


Fig. 24—Intraoral roentgenograms of patients with congenital syphilis, showing unerupted permanent central incisors and first molars. Note the convergence of the proximal surfaces and the smaller size of the teeth. *A*, The permanent central incisors are screwdriverlike; the permanent first molars are mulberrylike. Note the irregularity of the incisal third and the occlusal surface. *B*, Note the notch in the unerupted permanent upper central incisors. The permanent first molars are the bud form described by Pfluger. (B. G. Sarnat and N. W. Shaw: *Am. J. Dis. Child.*)

permanent teeth, which may be caused by other diseases occurring during the first year of life, must not be confused with the malformations produced by syphilis. Some examples of the deformities are illustrated by the following pictures and roentgenograms.

Nonspecific serological reactions have been observed by A. Hill.<sup>158</sup> In a group

of more than 26,000 infants and babies tested for syphilis there were 242 non-specific reactions. Among these were 37 patients who had positive or doubtfully positive reactions on one or two occasions but later had persistently negative reactions without any treatment. At least two-thirds of the patients of this group had acute or chronic infections, chiefly



respiratory, but occasionally such diseases as nephritis, rat bite fever, dysentery, poliomyelitis, and rheumatic fever, which were apparently responsible for temporary false positive reactions.

The *treatment* of 36 syphilitic infants and children with massive doses of *arsenic* has been carried out by I. M. Levin, S. J. Hoffman, D. S. Koransky, I. B. Richter, and B. Gumbiner.<sup>159</sup> Twelve patients were less than three

sen in doses of 1.6 mg. ( $\frac{1}{40}$  gr.) per pound of body weight a day for a period of five days and occasionally as much as 3 mg. ( $\frac{1}{20}$  gr.) per pound of body weight. On the first day of treatment, 10 per cent of the calculated dose was administered; on the second day 15 per cent, and on the third, fourth, and fifth days 25 per cent of the total dose. There were no serious reactions and no deaths. A reversal in serological reaction oc-

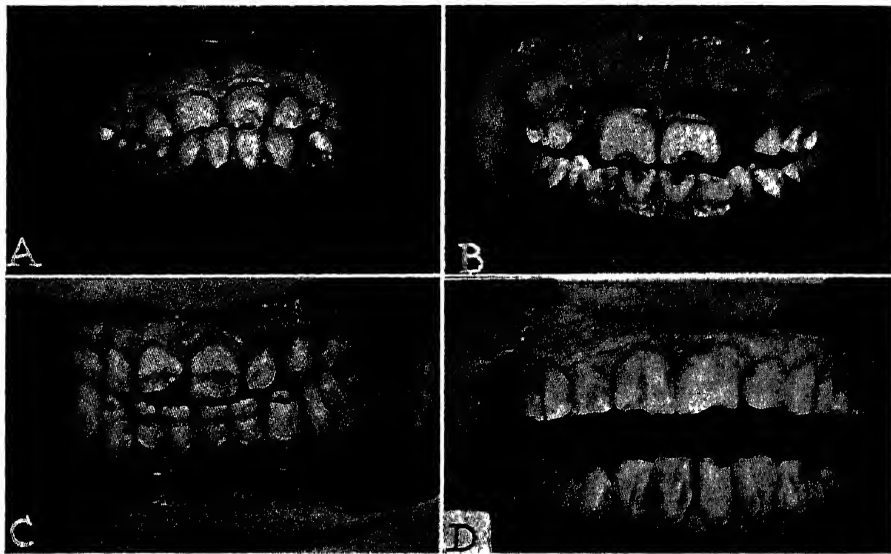


Fig. 25—Differential diagnosis of the Hutchinson incisor. *A*, Typical Hutchinson incisors, with convergence of the proximal surfaces and a notch of the midincisal edge. This was caused by a disturbance in dental development at about birth and shortly thereafter. *B*, Notched incisors due to lack of enamel formation (hypoplasia of enamel). This abnormality was caused by a disturbance in dental development when the child was about 3 to 4 months of age. *C*, Hypoplasia of the enamel due to a systemic disturbance between approximately 6 and 12 months of age. *D*, Notched incisors due to environmental rather than developmental factors (abnormal local wear of teeth [abrasion] due to repeated holding of nails between teeth by an upholsterer). The only lesion characteristic of and due to congenital syphilis is that shown in *A*. (B. G. Sarnat and N. W. Shaw: *Am. J. Dis. Child.*)

months of age. Before the treatment was instituted the patients were carefully examined to make sure that they were in good health and able to take food well. A preliminary course of *mercurial injections* was given every other day for a period of two or more weeks and *blood transfusions* were provided for those who were especially anemic. The arsenic therapy, given by continuous intravenous methods, consisted of *maphar-*

*sen* in doses of 1.6 mg. ( $\frac{1}{40}$  gr.) per pound of body weight a day for a period of five days and occasionally as much as 3 mg. ( $\frac{1}{20}$  gr.) per pound of body weight. On the first day of treatment, 10 per cent of the calculated dose was administered; on the second day 15 per cent, and on the third, fourth, and fifth days 25 per cent of the total dose. There were no serious reactions and no deaths. A reversal in serological reaction oc-

and after the treatment. The blood showed no evidence of reduction in number of platelets or white cells; there was no anemia; icteric indexes remained normal, and there were no significant changes in the levels of protein, nonprotein nitrogen, calcium, or phosphorus in the blood. The urine analyses showed no evidence of kidney damage and roentgenograms indicated a general improvement of the syphilitic condition. It was concluded by the authors that congenital syphilis, which had caused widespread damage to the tissues, did not respond as well to the massive intravenous therapy as did acquired syphilis, but results in the former condition were encouraging and the therapy required further study.

*Mapharsen* was administered intramuscularly to a number of children by G. D. Astrachan and V. Cornell.<sup>160</sup> The therapeutic results were satisfactory and the reactions were not numerous or severe. Some patients had considerable pain at the site of injection but none developed local necrosis or systemic symptoms. Mapharsen was administered in doses of 0.75 mg. ( $\frac{1}{80}$  gr.) per Kg. (2.2 lb.) of body weight, which seemed sufficient to bring about reversal of serologic reactions in a relatively large number of patients with congenital lesions and to heal certain lesions of the disease, notably interstitial keratitis. *Bismuth* was used in conjunction with the mapharsen therapy.

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## TETANUS

NINA A. ANDERSON, M.D.

Since the sulfonamides are only bacteriostatic, there is the possibility of future development of tetanus from *sulfonamide dusting powder* when the proper conditions for spore forms are made available. The sulfonamide may act as a tissue debilitant. H. Welch, G. G. Slocum, and R. P. Herwick<sup>161</sup> produced tetanus in guinea pigs treated with *sulfanilamide dusting powder* contaminated with washed tetanus spores. They emphasize that sulfonamide dusting powder must be sterile.

**Immunization**—J. V. Cooke and F. G. Jones<sup>162</sup> have concluded that large amounts of heterologous antitoxin inhibit the antigenic action of toxoid and only when such passive antitoxin titers have reached a relatively low level is active toxoid immunization effective. It has been stated that 1500 units of *tetanus antitoxin* will produce a protective titer lasting about three weeks. In human beings, clinical protection from

tetanus requires a titer of 0.01 to 0.1 unit of antitoxin from passive immunity, while in active immunity 0.001 to 0.01 unit is sufficient. In a group of eight children who had received treatment for tetanus with 100,000 units of antitoxin these authors found high early levels of antitoxin. There was as much as one unit remaining three to four weeks later, 0.1 unit six to ten weeks later, and 0.01 unit eight to 11 weeks later. In one case treated with 150,000 units of tetanus antitoxin, the high levels persisted even longer. Among a group of 21 who received 10,000 units of tetanus antitoxin in the treatment of tetanus, 14 had as much as 0.1 units four to six weeks later and 0.01 unit six to ten weeks later. In one case in which the blood level was 50 units on the third day, the spinal fluid level was only 0.2 unit, and on the ninth day when the blood level was 30 units, the spinal fluid level remained 0.2 unit. In another patient when the blood level

was 70 units, the spinal fluid level was 0.017 unit.

No immunity apparently follows an attack of tetanus. Four children who had had clinical tetanus showed no development of tetanus antitoxin when the first dose of toxoid was given some time after recovery. When given, intracutaneously or subcutaneously, 1 cc. of tetanus toxoid every two days for four doses, the titer was 0.003 or less for seven weeks of observation.

When four children were given 1 cc. of plain tetanus toxoid every two days for four doses and then 1 cc. of toxoid eight weeks later subcutaneously, while no antitoxin was developed in the blood following the first series, it appeared quickly after the stimulating dose of toxoid. To four other children 10,000 units of tetanus antitoxin were administered on the first day of a similar schedule of treatment. There was a progressive decrease in the (passive) antitoxin titer and the antitoxin disappeared entirely at the end of five weeks. The stimulating dose of toxoid did not produce any antitoxin within a period of two weeks. The same results were obtained whether the administration of toxoid was by the subcutaneous or the intracutaneous route. The same inhibition resulted in two children with clinical tetanus treated with antitoxin and given toxoid simultaneously.

When 10,000 units of tetanus antitoxin were given intramuscularly to healthy children and followed by 0.5 cc. of *alum precipitated toxoid* at the same time and every two weeks thereafter for six doses, or by toxoid two weeks later and then every two weeks later for five doses, or by toxoid four weeks later and then every two weeks for four doses, or by toxoid six weeks later and then every two weeks for three doses, active immunity did not begin to develop for eight

to 12 weeks. In all, a lower titer of the passive antitoxin was reached before the appearance of active immunity. Similar results were obtained in two cases which had been treated for clinical tetanus.

Two years after completion of basic immunization with two 0.5 cc. doses of *combined alum precipitated diphtheria and tetanus toxoids*, M. M. Peshkin<sup>163</sup> gave 18 children a third dose of 0.5 cc. of the combined alum precipitated toxoids and 13 children alum precipitated tetanus toxoid alone. Within one month adequate tetanus antitoxin titers were obtained, which were higher and lasted for a longer time than those which followed basic immunization as well as those which followed the third dose of combined toxoids given three to 15 months after basic immunization.

In a comparison of different methods of combined or simultaneous immunization for routine prophylaxis in infancy against diphtheria, tetanus, and whooping cough, J. H. Lapin<sup>164</sup> favors the use of three injections of *pertussis vaccine* monthly, followed by two injections of combined alum precipitated diphtheria-tetanus toxoids at two-month intervals. After 12 months, 13 per cent had fallen below a safe diphtheria antitoxic level of 1:250 unit per cc. and 13 per cent had fallen below the safe tetanus antitoxin level of 0.1 unit per cc. Pertussis agglutination and complement fixation tests remained just as high after 12 months as after the original three-month period. The comparison of serologic results and reactions from triple immunization of infants by various methods are given in Table XI, p. 593.

Among a group of children previously immunized with alum precipitated combined diphtheria and tetanus toxoid 1½ to 3½ years before, L. A. Yeazell and W. C. Deamer<sup>165</sup> found that 48 per cent of the 100 children had 0.1 unit and 91

TABLE XI

COMPARISON OF SEROLOGIC RESULTS AND REACTIONS FROM TRIPLE IMMUNIZATION  
OF INFANTS BY VARIOUS METHODS\*

Methods Tested	Num- ber of Cases	Schick Test (Negative in %)	Diphtheria Antitoxin Level in Blood (Units per cc.)	Tetanus Antitoxin Level in Blood (Units per cc.)	Whooping Cough		Reaction	
					Agglu- tination Test	Com- ple- ment fixa- tion	Fever (De- grees)	Local (Inches)
(1) 3 injections of clear diphtheria toxoid and 2 injections of alum tetanus toxoid and 3 injections of pertussis vaccine given separately ad seriatim	10	90.0	+0.07	+0.13	3.0+	2.5+	99.6	0.35
(2) 3 injections of pertussis, followed by 2 of diphtheria-tetanus toxoid alum-precipitated	10	100.0	+0.63	+0.49	3.2+	3.0+	99.7	0.25
(3) 3 injections of diphtheria - pertussis vaccine, alum-precipitated, followed by 2 of tetanus toxoid, alum-precipitated	10	80.0	+0.27	+0.09	2.5+	2.6+	100.9	1.7 and 1 abscess
(4) Simultaneous 3 injections of pertussis vaccine in 1 arm and 2 of alum-precipitated diphtheria-tetanus toxoid in the other	10	100.0	+0.23	+0.27	2.8+	2.1+	100.5	0.85
(5) Alum - precipitated combination of pertussis vaccine, diphtheria toxoid, and tetanus toxoid in 3 monthly doses	10	100.0	+0.47	+0.41	2.4+	2.9+	101.6	0.9 and 1 abscess
(6) Clear diphtheria toxoid, alum-precipitated tetanus toxoid, pertussis vaccine, and pertussis toxin in 5 monthly doses	78	100.0	+0.1	+0.5	3.9+	3.8+	101.5	1.0

\* J. H. Lapin: J. Pediat.

per cent had 0.01 unit or over. After a stimulating dose of 0.5 cc. of alum precipitated tetanus toxoid the titer of every child rose, somewhat in proportion to the prestimulation titer. One week after recall stimulation 51 per cent had three to 10 units. Among 20 other children who had received only two injections in the basic immunization 20 per cent had titers below one unit one week after the stimulating dose as compared with five per cent in the group who had received three injections for the basic immunization. Forty-five per cent of this group had a level of 0.1 unit or more after the recall injection; 90 per cent, 0.01 unit or more.

The injection of 0.1 cc. of plain tetanus toxoid intradermally caused a rapid rise in antitoxin titer above the basic levels in 12 subjects. Three of these showed a local reaction to the injection.

After the administration of 1500 to 4500 units of tetanus antitoxin, only three of ten patients had a titer of 0.1 unit or above in six to 15 days.

On the basis of these studies, the authors favor three injections of 1 cc. of combined toxoid plus a stimulating dose every two to three years and a recall injection of toxoid irrespective of the injury.

J. R. Gallagher, C. D. Gallagher, and

G. G. Kaufmann<sup>166</sup> have found it practical, safe, and desirable to administer alum precipitated tetanus toxoid to adolescents. To 509 boys, ranging from 13 to 19 years of age, they gave 1 cc. of alum precipitated tetanus toxoid, for two doses at four- to seven-week intervals. Initially, 0.1 cc. of 1:10 physiologic saline dilution of the tetanus toxoid was injected intradermally. If the test was quite positive in ten minutes, undiluted toxoid was given in divided doses of 0.1, 0.2, 0.3, and 0.4 cc. on four successive days. In the group 3.7 per cent had strongly positive skin tests; of these 36 per cent gave no history of allergy nor of previous administration of tetanus antitoxin. Fourteen per cent of those with asthma or hay fever had a positive skin test. There were no anaphylactic reactions, no serious local or systemic reactions among these patients. No significant differences were seen in the groups, but it is to be noted that the toxoid was administered in divided doses to those with positive skin tests. The authors concluded, however, that neither skin sensitivity to dilute tetanus toxoid nor a history of allergy was a reliable criterion on which to predict skin sensitivity or the development of local or systemic reactions.

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## TOXOPLASMOSIS

WALDO E. NELSON, M.D.

Toxoplasmosis, as a human infection, has been recognized only within recent years although the organism, a genus of protozoa, has been recognized since 1909. In retrospect there are several recorded human infections which may have been toxoplasmosis, but it was not until 1939 that Wolf, Cowen, and Paige established the existence of human infection with *Toxoplasma* by the experimental trans-

mission of the infection to animals from man and by the subsequent recovery of the organisms from the infected animals. Since this observation a number of other cases of toxoplasmosis have been recorded and the infection is now established as a definite clinical entity, although at the moment it is not possible to evaluate it from an epidemiologic standpoint. In general, the cases which

have been described can be divided into three categories: (1) A form occurring in young infants in which the symptoms appear shortly after birth and which has been termed "infantile encephalomyelitis" by Paige, Cowen, and Wolf.<sup>167</sup> It is assumed that in these instances the infection occurs *in utero*; (2) an atypical form of encephalitis in older children observed by Sabin,<sup>168</sup> and (3) the infections in adults recorded by H. Pinkerton and R. G. Henderson<sup>169</sup> in which the clinical features were quite different from those described in infants and children. The outstanding features were an atypical pulmonary involvement and general manifestations, including a rash which was quite similar to certain of the rickettsial infections and especially to Rocky Mountain spotted fever. An excellent survey of the present material on toxoplasmosis has been made by Sabin in "Advances in Pediatrics," Interscience Publishers, Inc., New York, 1942.<sup>170</sup> This article has been freely employed, in addition to those specifically cited, in the preparation of this review.

The epidemiologic data on *Toxoplasma* is far from complete, but it is known that a wide variety of animals is susceptible to it and that in some of them it occurs naturally. Natural or spontaneous infection has been observed in dogs, rabbits, guinea pigs, and a number of lesser known animals. Cats and mice have been shown to be susceptible and it is not unlikely that there is natural infection among them. The manner of the natural transmission of *Toxoplasma* to man or from animal to animal is not known. In both of the adult cases of Pinkerton and Henderson<sup>169</sup> there was a history of exposure to ticks. Sabin<sup>170</sup> suggests the probability that the infection may be transmitted by direct contact with infected tissues or excreta, or by flies, ticks, and so forth.

Illustration of the organisms of *Toxoplasma* are shown in Figs. 1 and 2. The parasites have a distinct cytoplasm and a nuclear chromatin, and their size and appearance vary with the stage of development and with the manner of examination. Examined in the fresh stage or in Giemsa or Wright stained films they vary in size from 4 to 7  $\mu$  in length and 2 to 4  $\mu$  in width.

Sabin<sup>170</sup> points out that the pathologic changes produced by *Toxoplasma* are determined by their apparently obligate intracellular parasitism. This is evidenced by the fact that: (1) Fully virulent *Toxoplasma* have affinities not only for the reticuloendothelial system, but also for a large variety of parenchymal cells; (2) *Toxoplasma* are distributed in the body by way of the blood, and (3) their localization in various organs appears to depend on their capacity to invade and grow through the blood vessels of the particular organ as well as on the special susceptibility of the parenchyma. In general, it would appear that in the fetus and during early infancy *Toxoplasma* chiefly produce marked destruction of nervous tissue, although there is evidence that they may also localize and occasionally produce lesions in other tissues and in the viscera. In the acquired infection in children, the central nervous system still appears to show the greatest involvement although the lesions related to the *Toxoplasma* may be minimal. In adults the lesions appear to predominate in the viscera. In the two cases examined by Pinkerton and Henderson<sup>169</sup> the outstanding feature was a peculiar type of interstitial pneumonitis. Meningoencephalitis, though present, was not conspicuous. Pathologic features common to the infantile and the adult type were focal brain lesions, myocarditis, and the presence of *Toxoplasma* in the lesions.

As stated above, the clinical cases which have been observed can, in general, be divided into three categories, which arbitrarily may be termed the infantile, the childhood, and the adult. Paige, Cowen, and Wolf<sup>167</sup> have now observed nine cases of the infantile type. The symptoms and signs in these instances began at birth or shortly thereafter, and in view of the chronic appearance of the pathologic lesions, which were often extensively calcified, it was considered most likely that the onset was during the intrauterine period. The possibility is also considered that congenital toxoplasmosis may not manifest itself clinically until late in infancy or in childhood. Sabin<sup>170</sup> has observed a case in which no abnormalities referable to toxoplasmosis were noted until the infant was six months of age. The diagnostic criteria for the infantile form as outlined by Paige, Cowen, and Wolf<sup>167</sup> are as follows:

"1. A history of onset of symptoms at birth or during early infancy.

"2. Varied neurologic symptoms, including convulsions and hydrocephalus (although these may be absent).

"3. Ophthalmoscopic observation of chorioretinitis, frequently in the macular region; yellowish white or reddish brown, round or oval, slightly depressed or elevated patches with irregular spotty black, often marginal, pigmentation.

"4. Roentgenographic demonstration of intracerebral calcification.

"5. Determination of clinically inapparent internal hydrocephalus by pneumonencephalography.

"6. Xanthochromia, round-cell pleocytosis, and high protein content of the cerebrospinal fluid (lumbar or ventricular).

"7. The recovery of *Toxoplasmas* from the blood or cerebrospinal fluid by inoculation of mice, rabbits, or both, intracerebrally and intraperitoneally.

"8. Demonstration of *Toxoplasma*-neutralizing antibodies in the blood of the infant or of the mother."

Data on eight additional cases have been collected from various sources by Sabin.<sup>170</sup> The children varied in age from seven months to 15 years and with one exception exhibited either cerebral calcification or chorioretinitis in the macular regions, or both, in addition to various other manifestations. In all instances there were positive neutralization tests from the sera of the patients and from their mothers. In contrast, neutralization tests on eight children with hydrocephalus and two infants with microcephaly who had neither cerebral calcification nor chorioretinitis were all negative. Of further interest are the data on women who had given birth to infants with hydrocephalus or microcephalus, or to anencephalic monsters. Three of four women, who gave birth to hydrocephalic (three) or microcephalic (one) infants, who were either stillborn or died shortly after birth had neutralizing antibodies against *Toxoplasma*. Among eight women who gave birth to anencephalic monsters, three (without hydramnios) had neutralizing antibodies against *Toxoplasma* and negative Wassermanns, two (without hydramnios) had positive Wassermanns and negative *Toxoplasma* tests, and the remaining three (with hydramnios) had negative tests. These observations add support to the belief that toxoplasmic infection during intrauterine life may be a cause of hydrocephalus and perhaps of other intracranial abnormalities.

The data on acquired childhood infection are based on the two cases of Sabin.<sup>168</sup> The first case occurred in a six-year-old boy in whom the onset was with severe headache, and in the course of the following week there were several generalized convulsions, vomiting, and unsteady gait with weakness of the extremities, all without any history of fever. At the time of admission to the



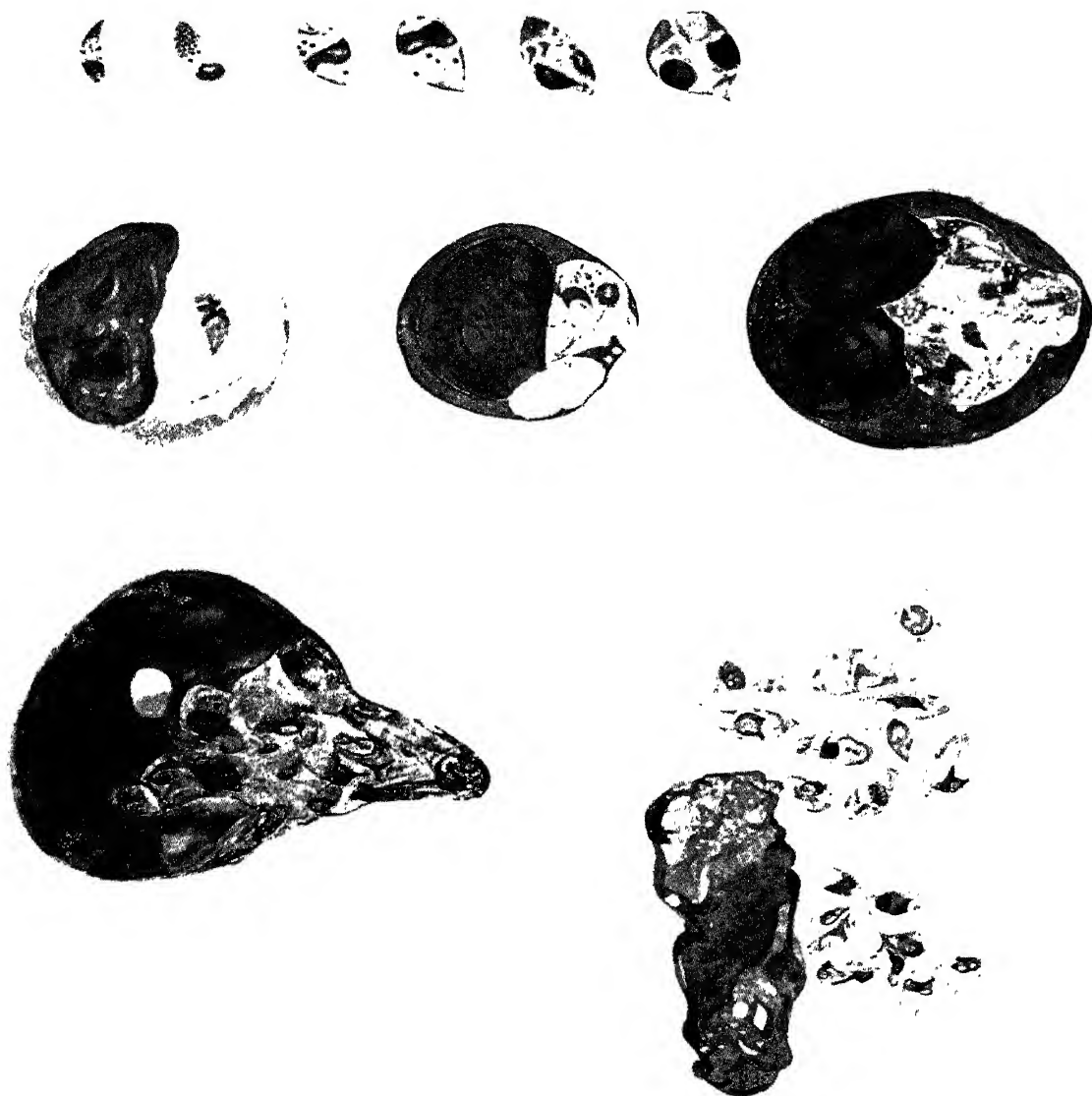


Fig. 26—Drawing showing stages in growth and multiplication of virulent strain of *Toxoplasma*.  
(Sabin, A. B.: "Toxoplasmosis," in DeSanctis, A. G., Ed.: *Advances in Pediatrics*.)



hospital he did not appear to be acutely ill, and the neurologic examination was remarkable for the negative rather than for the positive findings. There was no stiffness of the neck or spine and the Kernig and Brudzinski signs were negative. The reflexes and sensation were not abnormal and there were no signs of

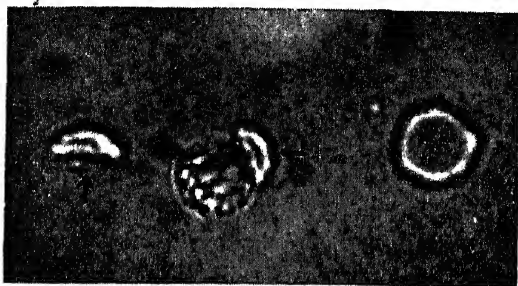


Fig. 27—*Toxoplasma* in fresh state; mouse peritoneal exudate. (Sabin, A. B.: "Toxoplasmosis," in DeSanctis, A. G., Ed.: *Advances in Pediatrics*.)

involvement of the cranial nerves. The fundi were normal. There was a palpable spleen, generalized lymphadenopathy, and 30 mononuclear cells per c.mm. of spinal fluid. Very shortly, however, he became delirious, began to have continuous twittings of various muscle groups, had occasional convulsions, and remained irrational, confused, and speechless un-

til his death on the thirtieth day of the illness. The number of cells in the spinal fluid increased until they reached 2200 per c.mm. with predominantly mononuclear cells. The protein and sugar content of the spinal fluid were not abnormal.

The second case was that of an eight-year-old boy who had signs of encephalitis for only ten days and made a complete recovery without any sequelae. The symptoms included vomiting, generalized convulsions, and a state of confusion for one day. The neurologic examination was negative except for the spinal fluid which contained 200 to 300 cells per c.mm. and were mostly lymphocytes. The diagnosis was made from the isolation of *Toxoplasma* by inoculation of guinea pigs with the spinal fluid.

Two fatal cases of *Toxoplasma* infection in adults were recorded by Pinkerton and Henderson.<sup>169</sup> Both cases were characterized by fever, skin rash, and atypical pulmonary involvement. Death was apparently due to the respiratory embarrassment. Both clinically and pathologically the cases showed similarity to Rocky Mountain spotted fever,

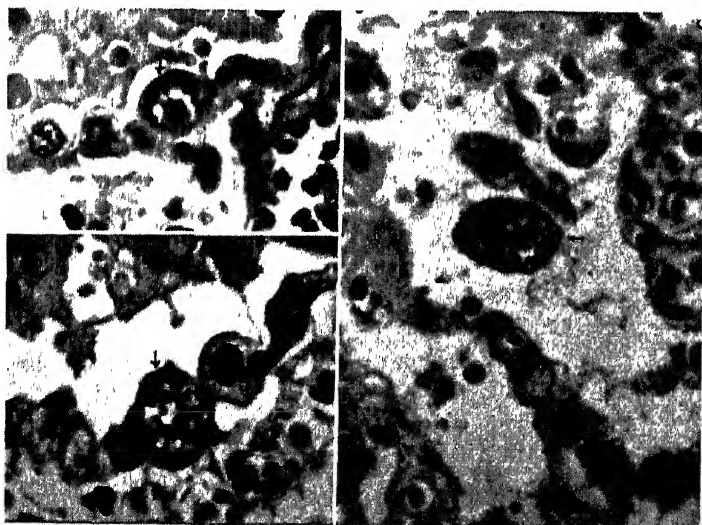


Fig. 28—Sections of lung from a case of toxoplasmic pneumonitis (adult) showing alveolar lining cells distended with *Toxoplasma* in (a) and (b) and a pseudocyst in the alveolar exudate in (c). (Sabin, A. B.: "Toxoplasmosis," in DeSanctis, A. G., Ed.: *Advances in Pediatrics*.)



Fig. 29—Cardiac muscle fiber in longitudinal section containing fusiform collection of Toxoplasma. H. and E.  $\times 780$ . (Sabin, A. B.: "Toxoplasmosis," in DeSanctis, A. G., Ed.: *Advances in Pediatrics*.)



Fig. 30—Cerebral calcification in a 10-year-old boy presenting microcephaly, healed chorioretinitis in the macular region of both eyes (very poor vision), mental retardation, and a history of recurrent "attacks" (since  $2\frac{1}{2}$  years of age) characterized by: Seeing spots before his eyes, followed by dimness of vision, headache, nausea, drowsiness and recovery without loss of consciousness or convulsions after vomiting. Toxoplasma neutralization tests positive on patient and his mother. (Foci of calcification retouched.) (Sabin, A. B.: "Toxoplasmosis," in DeSanctis, A. G., Ed.: *Advances in Pediatrics*.) (Reproduced by courtesy of Dr. Bronson Crothers and with the permission of the Children's Hospital, Boston, Mass.)

and it is of some interest that in both of these cases ticks had been removed from the patients before the onset of the acute symptoms. In one of these cases the fever at the time of admission to the hos-

pital was  $106^{\circ}$  F., and there was a maculopapular eruption covering the entire body except the scalp, the palms of the hand, and the soles of the feet. There were coarse râles and dullness over both

lung bases. The roentgenogram of the chest showed scattered, irregular areas of increased density in both lower lung fields as well as accentuation of the lung markings and hilar shadows. The temperature ranged at about 103° and 104° F. *Toxoplasma* were found in sections of the lungs, heart, and spleen of this case.



Fig. 31—Chorioretinitis in a 4-year-old child presenting defective psychomotor development and repeated major convulsions since 6 months of age. Diagnosis of congenital toxoplasmosis supported by demonstration of neutralizing antibodies in child and mother. (Sabin, A. B.: "Toxoplasmosis," in DeSanctis, A. G., Ed.: *Advances in Pediatrics*.) (Reproduced by courtesy of Dr. Douglas N. Buchanan of the University of Chicago.)

A fourth type of clinical infection is suggested by Sabin<sup>170</sup> as a mild or inapparent infection evidenced only by the possession of antibodies against *Toxoplasma*, or by the giving birth to an infant with clinically apparent toxoplasmosis.

The clinical diagnosis depends upon the clinical pattern just described and, more specifically, by demonstrating the organisms of *Toxoplasma*, by inoculation of properly selected animals, and by the demonstration of neutralizing antibodies

from three to four weeks after the onset of illness.

To date, there is no specific therapy, and the treatment is symptomatic. In the acquired cases, Sabin<sup>168</sup> suggests that *sulfapyridine* or *sulfathiazole* (other sulfonamides except sulfanilamide have not been tested) may be justifiably employed. On the basis of animal experimentation, little can be expected from *sulfanilamide*.

## TUBERCULOSIS IN INFANTS AND CHILDREN

**Congenital Transmission**—Of considerable importance to the question concerning the possibility of congenital infection with the tubercle bacillus is the experimental work of H. J. Corper and M. L. Cohn.<sup>171</sup> A relatively large intravenous (0.01 mg.) injection of highly virulent human tubercle bacilli into a pregnant guinea pig did not result in the passage of the bacilli to the fetus during a period up to nine days and possibly for one as long as 12 days. Such passage did not occur in spite of the fact that the mother guinea pig succumbed to the intravenous virulent infection within one to two weeks after birth of the offspring.

The offspring from the heavily intravenously infected mother guinea pig did not develop any discernible specific tuberculo-immunity, as determined by infection tests, nor specific tuberculin hypersensitiveness, as measured by the skin tuberculin reaction.

In spite of the fact that viable avirulent human tubercle bacilli injected intravenously in amounts as high as 1 mg. produced an excellent specific tuberculo-immunity and a definite specific tubercule-allergic hypersensitiveness to tu-

berculin in the mother guinea pig and that there was plenty of time *in utero* for the passage of this specific tuberculo-immunity and specific allergic-hypersensitiveness, no evidence of such passage to the offspring was noted.

#### **Determination of Clinical Activity**

—An interesting observation on the disparity between oral and rectal temperatures after exercise has been recorded by J. Brennemann.<sup>172</sup> It is pointed out that temperatures taken by rectum average about 1° F. higher than those taken by mouth. It is also generally recognized that the body temperature may rise several degrees with exercise, the elevation varying directly with the amount or intensity of the exertion. It is apparently not widely known, however, that exercise will cause the rectal temperature to go up several degrees while the oral temperature taken at the same time may remain unchanged, rise slightly or, as often, fall to a lower point. The rise in rectal temperature and the variations of the oral were directly proportional to the intensity of the exercise. Both temperatures returned to normal in 30 to 60 minutes.

There are definite clinical implications in this observation. Obviously, rectal temperatures should be evaluated without exercise and not after it. And in those instances in which fever is observed only after exercise and for which no other cause is found, it should be considered a normal phenomenon. This factor should be especially kept in mind in the evaluation of children who are recovering from such chronic illnesses as tuberculosis and rheumatic fever, and if there are no other abnormal factors, increase of rectal temperature after exercise cannot be accepted as an evidence of activity of disease.

**Bronchial Tuberculosis** — A series of infants and small children in whom

tuberculosis was the cause of mechanical obstruction in the bronchial passages has been reported by J. Meneghello and C. A. Smith.<sup>173</sup> It is pointed out that, in most infants and children who have primary tuberculous lesions, the extent of the lymph node involvement exceeds that of the area of primary lung infection. The anatomic association of these nodes with the bronchi offers an obvious opportunity for mechanical interference with respiration. Such interference may be the result of external compression or ulceration through the bronchial wall and of the formation of a mural mass of tuberculous granulation tissue from which actual cicatricial stenosis of the bronchus may occur. These lesions may occur as individual entities or in various combinations.

In this series it was evident that tuberculous processes could produce either atelectasis or emphysema, depending on the completeness with which the air passages were obstructed, and that either atelectasis or emphysema could succeed the other in the same child. Of interest was the fact that evidences of obstruction were often the major and, in some instances, the only evidences of illness. Such lesions were found much oftener in younger children and infants than in older ones.

Bronchoscopic examination is recommended as a diagnostic procedure since it determines whether the obstruction is produced by extraneous pressure or by intrabronchial granulation tissue. No other specific type of therapy is recommended, and treatment need only be the general hygienic care of the tuberculous child. Although collapse or emphysema may remain for six months or more, the ultimate outcome in this series has been one of complete recovery in the majority of infants. Longstanding collapse of a lobe due to complete bronchial obstruc-



Fig. 32—Case 1. Upper left. Admission film, July 20, 1940. (E. M. Jones, T. N. Rafferty, and H. S. Willis: *Am. Rev. Tuberc.*)

Fig. 33—Case 1. Upper right. Film 3 weeks after admission (August 10, 1940) when patient was acutely ill. (E. M. Jones, T. N. Rafferty, and H. S. Willis: *Am. Rev. Tuberc.*)

Fig. 34—Case 1. Lower left. Film taken August 24, 1940, after further exacerbation. (E. M. Jones, T. N. Rafferty, and H. S. Willis: *Am. Rev. Tuberc.*)

Fig. 35—Case 1. Lower right. Film taken September 28, 1940, 2 days after removal of tuberculoma. (E. M. Jones, T. N. Rafferty, and H. S. Willis: *Am. Rev. Tuberc.*)



tion resulted in clinical findings which might possibly have been those of bronchiectasis in only one of seven children who could be followed after such a process.

Further evidence that many of the consolidated tuberculous lesions of the primary infection are atelectatic and result from bronchial distortion or disease which is produced by direct continuity from the peribronchial lymph nodes is presented by E. M. Jones, T. N. Rafferty, and H. S. Willis.<sup>174</sup> These lesions have in recent years been termed "epituberculosis," a term which many have for some years thought ought to be discarded. The hypothesis presented to explain the consolidated lesions is that the atelectatic lobules or lobar areas result from interference with pulmonary aeration and drainage; this interference arises during the active phase of the primary complex and most frequently is a direct result of extension of the tuberculous process into the bronchial wall from the infected peribronchial lymph nodes. In 31, or 74 per cent, of the author's series, bronchial distortion or disease was present chiefly as narrowing of the lumen from pressure by enlargement of the root, tuberculoma, or ulceration. Edema, redness, and secretions were present in many of the cases. In some instances more than one of these conditions was present. In Figs. 32, 33, 34, and 35, a series of roentgenograms of one of their cases is shown in which partial but rapid clearing followed the partial removal of a tuberculoma and the aspiration of thick secretion through the bronchoscope.

**Tuberculin**—A new method for performing the tuberculin test has been described by H. Vollmer, H. W. Hyslop, and H. V. Lomant.<sup>175</sup> The test is, in actuality, a modification of von Pirquet's method in which a skin abrasive is com-

bined with the tuberculin test substance. Pumice was chosen since it is a porous, volcanic substance rich in capillary spaces and is an effective abrasive as well as a powerful absorbent.

Pumice particles having a diameter of about 0.1 mm. are attached to the ends of wooden applicators 8.2 cm. long with Duco cement in such a way that only the proximal parts of the particles are embedded and their capillary spaces filled with the cement substance. The free ends

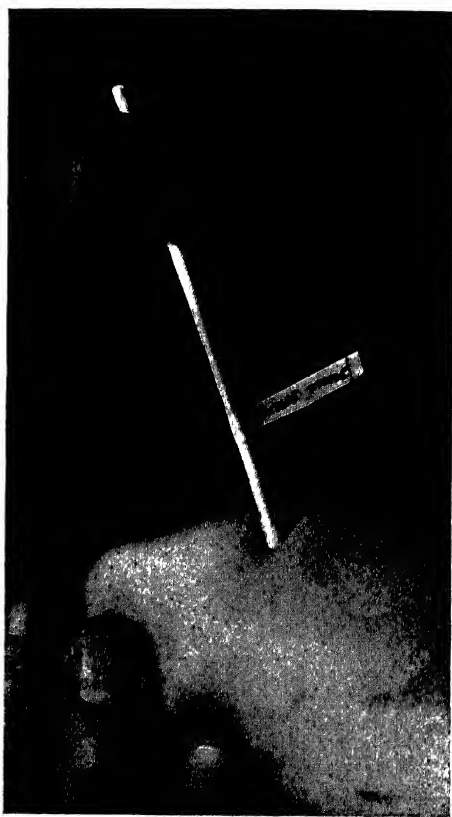


Fig. 36—The match test is placed perpendicularly on the stretched skin and 2 or 3 turning movements are carried out between the index finger and the thumb. (H. Vollmer, H. W. Hyslop, and H. V. Lomant: *J. Pediat.*)

of the pumice particles do not come into contact with the cement and thus retain unimpaired absorbent capacity. After complete drying of the cement, the head of the applicator containing the firmly attached pumice particles is dipped into old tuberculin. This simple instrument

resembles a match and may be called the "match test."

The skin of the inner surface of the forearm is stretched, the match test perpendicularly placed on the skin, and, under very slight pressure, two or three turning movements are carried out between the index finger and thumb (Fig. 36). This produces a rather painless, scarcely visible abrasion resulting in a circular area about 2 mm. in diameter.

Among 51 tuberculous children who were positive reactors to the patch test and to the Mantoux test with 0.1 mg. of old tuberculin, 48 had a positive and three a negative reaction to the match test. It is concluded that the tuberculin match test is equivalent to the Pirquet test, but has no advantages over the tuberculin patch test.

A "visible tuberculin patch test" has been devised by M. Grozin,<sup>176</sup> which overcomes the disadvantage of the tuberculin patch test, that the area of reaction is concealed while the patch is in place. The modified patch test is constructed as follows: Three incomplete circles are cut on a strip of adhesive plaster, forming flaps or lids, with the lower poles acting as hinges (SEE: Fig. 37). The two outer lids are treated with tuberculin, the middle lid, without tuberculin, acts as a control. The entire strip is applied to the skin. The areas of reaction are observed by lifting the lids.

The advantages claimed for the visible tuberculin test are: It is possible to view the results at any time without removing the strip. This may shorten the period required for reading the reaction as well as prevent some untoward local and systemic effects resulting from prolonged contact of tuberculin and adhesive plaster with the skin. On the other hand, if the results are doubtful, the strip can be kept on the skin for a longer time, and

repetition of the entire test may not be necessary.

From a small series of cases, P. J. Howard, J. A. Johnston, and C. L. Mitchell<sup>177</sup> have concluded that a rise to a high level of sensitivity to tuberculin

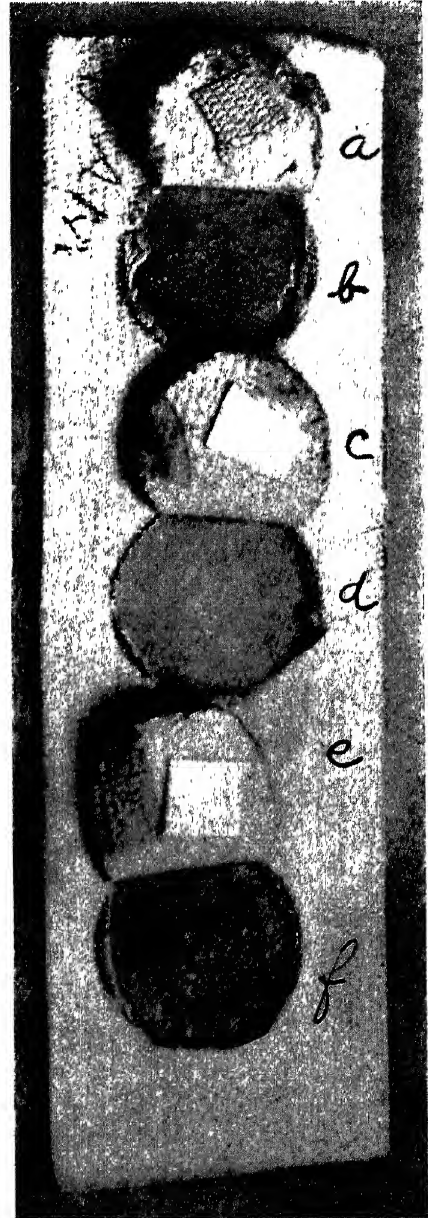


Fig. 37—Visible tuberculin patch test. Test strip in use: *a*, Everted lid which has previously been treated with tuberculin; *b*, positive cutaneous reaction; *c*, everted lid not treated with tuberculin (used as a control); *d*, no reaction; *e*, everted lid previously treated with tuberculin; *f*, positive reaction. (M. Grozin: *Am. J. Dis. Child.*)

with a subsequent fall is characteristic of the evolution of the healing process in bone tuberculosis, and that sustained high levels of allergy have characterized lesions which have shown a failure to heal.

**Immunity**—The effect of BCG immunization upon experimental pulmonary tuberculosis in the dog has been studied by S. D. Gunn, J. J. Sheehy, C. A. Colwell, and M. A. Mills.<sup>178</sup> The effects of intrabronchial inoculation with virulent tubercle bacilli were compared in two groups of dogs. One group had previously been inoculated intravenously, subcutaneously, or intrabronchially with living culture of attenuated tubercle bacilli (BCG); the other group had not been previously vaccinated and served as controls. The mortality attributable to tuberculosis was the same in vaccinated dogs as in unvaccinated controls. The average survival time in dogs which died of tuberculosis was longer in vaccinated than in controls, but the individual differences were so great that the averages probably had no significance.

No consistent differences in the size or composition of the pulmonary lesions in members of the two groups, examined at various intervals from the time of inoculation, were observed. Caseation and cavity formation occurred with about equal frequency in the two groups but caseation was slightly more extensive in the primary lesions of the unvaccinated dogs. The degree of hypertrophy, hyperplasia, and caseous necrosis of tracheobronchial lymph nodes was greater in controls than in vaccinated dogs during the first two-month period, but after this time these differences tended to disappear.

These observations would appear to indicate that the natural resistance of young or fully matured dogs to this form of tuberculous infection, which is of a very high order, cannot be further enhanced by injections of living attenuated tubercle bacilli (BCG), even though specific antibodies are present in the serum and hypersensitivity, as indicated by dermal reactivity to tuberculin, is developed to a considerable degree.

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## WHOOPING COUGH

ROBERT A. LYON, M.D.

**Diagnosis** — For the diagnosis of whooping cough, nasopharyngeal cultures proved to be superior to cough plates in the experience of A. M. Brooks, W. L. Bradford, and G. P. Berry.<sup>179</sup> The nasopharyngeal cultures of 61 per cent of a group of 248 patients were positive as compared with 37 per cent of a group of 167 patients tested with the cough plate method. In 165 instances in which simultaneous cultures were made, positive results were obtained in 57 per cent by the nasopharyngeal method and in 34 per cent by the cough plate method. The technic of taking the nasopharyngeal cul-

ture consisted of the use of a cotton swab wrapped about a fine copper wire which could be passed back through the nasal passage of one side until the posterior pharyngeal wall was reached. The secretions on the swab were mixed with a drop of physiologic saline solutions placed on the surface of Bordet medium and this mixture was streaked over the plate with a flexible wire loop. The plate was incubated for 72 hours. Sterile swabs were always ready for use and were kept moist by storing them in test tubes plugged with rubber stoppers.

A skin test employing an agglutininogen has been devised as a test of a patient's immunity by H. M. Felton and E. W. Florsdorf.<sup>180</sup> According to these authors the antigenic structure of the pertussis bacillus includes an agglutininogen and two toxins, one of which is more labile than the other. When the toxin is used in skin testing susceptible individuals, it produces delayed positive reactions which have not been considered accurate measurements of the patient's immunity. Agglutininogen was employed in testing some children who had had no contact with pertussis, others who had received prophylactic vaccination, those who had a history of previous attack of pertussis, and finally those with uncertain histories. The tests reflected with considerable accuracy the patient's experience with the disease. There were two types of response, the immediate wheal-like reaction and the delayed reaction simulating a tuberculin test, and some children showed both types. Two readings were recorded, one about one-half hour after the injection and the other 24 hours later. A positive reaction, which indicated immunity, usually consisted of an indurated area with or without erythema, 20 mm. or more in diameter, which appeared either after one-half hour or 24 hours or both. The weakly positive reaction which indicated some immunity consisted of an indurated area of about the same size or less occurring either at one-half or 24 hours after. The negative reaction which indicated susceptibility to the disease consisted of no reaction or an area of induration less than 10 mm. in diameter at any time. The response therefore of an immune patient was of the nature of an allergic reaction. The authors also noted that the injection of the skin test dose caused some increase in the patient's antibody titer, and therefore served as a mild stimulating dose of antigen.

With repeated doses even patients who were entirely negative developed some immunity within a short period of time.

**Prevention** — The prevention of whooping cough by the administration of vaccine has been carried out with considerable success by J. F. Coppolino.<sup>181</sup> One group of 152 children received the vaccination and another of 160 untreated children served as a control series. Both groups were observed over a period of more than four years. During this period of time the attack rate in the untreated group was about 85 per cent, while only seven per cent of those who were vaccinated contracted the disease, generally in a mild form. In six instances a vaccinated and an untreated child were exposed to the same case of whooping cough and in every case the vaccinated patients escaped the disease and the unvaccinated contracted the infection. The author observed that the immunization instituted at the age of seven months seemed to persist from three to four years or more.

A stimulating dose of whooping cough vaccine administered about two years after the initial vaccination increased the immunity of the majority of 41 children observed by K. M. Howell, E. J. Denenholz, M. Janota, and R. Stanard.<sup>182</sup> They employed the opsonocytophagic test as a measure of the immunity. Titers of immunity had generally dropped to a low level two years after the initial vaccination but the stimulating dose caused a rise which was maintained for the next  $2\frac{1}{2}$  years. Two cubic centimeters of pertussis vaccine were employed as the stimulating dose.

Whooping cough during the first few weeks of life when it is an especially dangerous disease may probably be prevented by giving the mother vaccine in the latter months of pregnancy. P. Cohen and S. J. Scadron<sup>183</sup> advised the admin-

istration of sufficient vaccine to include 150 billion organisms. It may be administered in small doses at intervals of two weeks, beginning about the sixth month of pregnancy and ending about two weeks before term. Such treatment produced local irritation in the majority of instances but none of the mothers developed serious reactions and there were no unfavorable effects on the course of the pregnancy nor on the time of delivery. The antibody titers, measured by mouse protection tests, were raised in the mothers and infants. The antibodies had apparently passed through the placenta without difficulty but further study of the infants was in progress to determine the extent and duration of the immunity.

Pertussis antibodies were developed in high titers in a group of pregnant women treated by L. Mishulow, L. Leifer, C. Sherwood, S. L. Schlesinger, and S. R. Berkey.<sup>184</sup> A group of 29 women who were in the third trimester of pregnancy received injections of 1 cc. of toxin-vaccine containing 10 billion bacilli and the injections were repeated at intervals of two weeks until 50 to 90 billion bacilli had been injected. The blood was examined at the time of delivery. None of the patients had received vaccine previously and about half of the group had had the disease in childhood but only 10 per cent had some protective antibodies before the treatment was started. At the time of delivery all had protective antibodies as measured by mouse protection tests. Ninety-three per cent had agglutinins and 76 per cent had complement fixing antibodies. There were no severe reactions and pregnancy did not seem to offer any contraindication or impediment to vaccination.

Agglutinins were demonstrated with regularity in the blood sera of vaccinated children by J. J. Miller, Jr., R. J. Silverberg, T. M. Saito, and J. B. Humber.<sup>185</sup>

Of a group of 215 children ranging in age from six to 36 months who had received vaccine containing 80 billion pertussis bacilli only five had no demonstrable agglutinins. There was a tendency for the titer of these antibodies to remain elevated for a period as long as six years after immunization. The authors noted that variations of the length of intervals between injections did not affect the agglutinin response but doses of 50 billion or less failed to stimulate antibody formation in many instances. Larger initial doses of vaccine did not cause higher agglutinin titers. A stimulating dose of vaccine administered a year or more after the first course of treatment usually caused high agglutinin levels in the blood serum.

The antibody content of the sera of vaccinated children was compared with the incidence of clinical infections of pertussis. A fairly close correlation was found between the presence of agglutinins and immunity to the disease. In some cases immunity was present when no agglutinins were discovered. Among 79 children intimately exposed to pertussis ten developed the disease. All of these had no or small amounts of agglutinins. Of the other 69 there were 46 with high titers. The agglutination measurement is therefore not an accurate test of a child's immunity but is an indication of the initial response to immunization and the degree to which immunity persists.

A pertussis toxoid has been used for prophylactic immunization and pertussis antitoxin has been used for therapeutic purposes by J. G. M. Bullowa, J. Alterman, N. Katona, M. Scannell, and A. Robinson.<sup>186</sup> The toxin derived from cultures of the pertussis bacillus was modified by the addition of formalin. The resulting toxoid, administered to 135 children, stimulated the production of an

antitoxin which was measured by means of skin tests in rabbits. Administration of toxoid to children who were in the active stages of the disease produced no results which changed the general course of the infection. The administration of antitoxin prepared from rabbit serum was also of very little value in reducing the severity of the disease when it was administered during the active stages of the infection, but when it was given to children who had been intimately exposed to the infection it seemed to have definite effect in preventing the occurrence of the disease. This immunity persisted throughout the period of exposure to the active infection.

Although a toxin has been isolated from cultures of the pertussis bacillus it was questionable to M. Weichsel, N. Katona, and F. Liu<sup>187</sup> whether the human body develops an antitoxin as one of its immune reactions to pertussis. The quantity of antitoxin in the blood was determined from the amount necessary to protect mice from injections of a lethal dose of toxin. Adults who had had pertussis in childhood and patients who had recently recovered from the disease had little or no antitoxin in their blood sera. A few children who were just recovering from the disease developed small amounts of antitoxin in their blood. Children who had been treated with detoxified toxin had relatively high titers of antitoxin in the blood. The usual vaccines used for the prevention of the disease did not simulate antitoxin. Antitoxin therefore did not seem to play an important part in the resistance to or recovery from the disease. However, some of the clinical symptoms of the infection appear to be toxic in nature and the possibility that an antitoxin might help combat these symptoms should be considered.

Toxin is not a satisfactory agent for testing the immunity of a patient and

probably antitoxin does not enter very prominently into the immune response of an individual in the experience of E. W. Flosdorf and A. C. McGuinness.<sup>188</sup> The pertussis bacillus produces two toxins—one of which is thermolabile and the other thermostable. However, the protection against pertussis resulting from the use of vaccine is due to the production of antibacterial substances in the blood stream of the patient and not to antitoxin. Hyperimmune serum, which seems to be effective in the treatment of pertussis, does not contain antitoxin. It is likely therefore that the resistance to pertussis is due to a bacterial antibody rather than to antitoxin.

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## PHYSICAL THERAPY

JOHN S. COULTER, M.D.

### CHRONIC ARTHRITIS

According to Piersol,<sup>1</sup> the procedures in physical therapy that are readily available to all physicians include massage, exercise, the application of heat and light, and hydrotherapy. Radiation therapy and electrotherapy are highly technical procedures, which are less easily carried out because their proper and safe use requires special training.

In properly selected cases, experience has shown that suitably applied physical therapy has been a useful and often a most important adjunct in their management. Into this category fall first the arthritides and allied rheumatoid dis-

orders. The employment of physical therapy in the treatment of rheumatic conditions is no innovation, since there is abundant evidence that even during antiquity it was extensively used for such conditions and its value was well recognized. Today physical therapy constitutes one of the most effective means at our disposal for the management of arthritis, especially of the chronic forms in their early stages.

Of the mechanical procedures of proven value in the treatment of arthritis, massage comes first. According to Pember-ton, "one of the most valuable measures in the treatment of arthritis and one of

the oldest therapeutic agents in the history of medicine is massage, with its associated variations."

Until comparatively recently, the physiology of massage was little known and its application was largely empiric. Today, the mechanism which underlies the beneficial effects of massage, although far from settled, is much better understood, thanks to the work of a number of investigators. It has been demonstrated that massage has no significant influence on general metabolism. Even after vigorous massage, there is no production of lactic acid in the muscles or the acidosis observed after exercise, nor does massage bring about the loss of lactic acid and alkalosis described after the application of heat. The outstanding effects of massage are due to changes brought about in the local circulation of the parts involved. These changes in turn are due to alterations in the capillary circulation, in which massage causes an increased rate of blood flow and alterations in the vessel walls that permit an accelerated interchange of substances between the blood and the tissue cells, with resulting improved metabolism.

The effectiveness of massage depends largely on its prolonged and systematic use. Its beneficial effects are most apparent in chronic conditions. For that reason, it is not a therapeutic agent that commands much attention in the treatment of the acute forms of arthritis. Its greatest value, when properly applied and systematically carried out, is found in the chronic hypertrophic or atrophic types of arthritis.

The indications for massage in arthritis, according to Pemberton, are fourfold: First, to prevent or delay atrophy of muscles and to help to restore muscle tissue when atrophy has occurred; second, to improve the general and local metabolism; third, to increase the extent

to which the circulating blood reaches certain tissues and to facilitate the return to the circulation of many corpuscular elements tucked away in inactive regions, and, fourth, to reduce local edema by mechanically replacing the effect normally exercised by muscles in aiding the heart to empty the venous circulation.

Massage is of value in chronic arthritis, not only because of its effect on the local conditions but because general massage increases the bodily vigor and in persons incapable of much activity improves general nutrition and metabolism. In this, as in all other conditions, massage should be applied intelligently and under the direction of a physician. Therefore, it is regrettable that in this country, at least, few physicians possess an adequate first-hand knowledge of massage and its various modifications. As a consequence, the application of this time-honored and useful procedure is too often delegated to lay technicians. Even with little or no technical knowledge, the careful physician should be alert to the contraindications and ill effects of massage. He should be prompt to observe any unfavorable manifestations, particularly undue fatigue, the occurrence of pain in muscles and joints, and other evidences of increased inflammatory reactions.

Exercise also has a definite place in the treatment of arthritis. When the arthritic patient has reacted favorably to general and local massage, the acute manifestations have subsided, and convalescence has been established, active motion, carefully regulated and controlled, should be instituted, especially when there are evidences of limitations of motion. No form of passive exercise can achieve the same beneficial results for an arthritic patient as exercise which involves a definite muscular effort on the part of the patient, provided always that

such exercise is kept well within the limits of the patient's potentialities.

Next to massage, the application of some form of heat constitutes one of the most useful physical therapeutic procedures in the treatment of arthritis. An ever-increasing number of thermotherapeutic appliances are available for the application of heat in one form or another. The application of heat in arthritis may be general or local. In whatever way heat is applied, its immediate effect is to raise the temperature of the body tissues. The extent to which the rise in temperature occurs depends entirely on the degree, extent, and duration of the application. The general application of heat in its milder forms is invariably accompanied by sweating. The local effects of heat are dilatation of blood vessels, an increased rate of blood flow accompanied by increased local metabolic activity, alkalosis, and probably accelerated phagocytosis, which increases local tissue immunity.

In chronic arthritis, the systemic use of heat has frequently been employed. The general application of heat is by no means suitable for all patients. Those who are to receive this type of treatment should be carefully selected. In general, the overnourished, middle-aged, robust type of person stands this form of treatment better than the patient who is debilitated, underweight, and old. The commonest methods of applying systemic heat to the arthritic patient are the hot bath, the hot pack, and various types of electrically heated cabinets. Patients receiving such treatments should be carefully observed, and the sweating process should never be too long or too severe. This type of treatment has enjoyed much popularity, because of the well-established belief that the successful treatment of arthritis depends on "elimination" and the misconception that the diaphoresis

induced by heat is a means of ridding the body of various toxic products. It has been shown that blood urea nitrogen, uric acid, and creatinine, as well as the non-nitrogenous constituents of the blood, are little if at all affected by sweating. The only substances that are eliminated are water and electrolytes. When their loss is excessive, dehydration and hypochloremia may result. In some instances the loss of water may be of advantage to the arthritic patient, but the chief value of the systemic application of heat in arthritis is due to the increase in circulation and metabolism that is brought about.

The local application of external heat to the joints of the patient with chronic arthritis has a wide and useful application. Local heat may be applied by conduction when heated objects are brought in direct contact with the body, such as a hot-water bottle, hot brick, hot compress, or the more elaborate electrically heated pad, paraffin packs, and other devices. Local heat may be applied as radiant heat or by convection, the surface of the body being heated by some external source, such as incandescent lamps placed in reflectors or coils or other forms of non-luminous heating appliance. When heat is applied by convection, it is developed in the tissues of the body by reason of their resistance to the passage of a large amount of high-frequency electric current. The physiologic effects of these different forms of local heat are essentially the same, with this exception, that conductive heat penetrates but little below the surface of the body and convective heat penetrates the skin layers and may even penetrate to some extent into the subcutaneous fat. On the other hand, the dull glow from coils is largely absorbed in the superficial layers of the skin. Convective heat produces the greatest amount of penetration. The use of local heat is not without its dangers, and the possibili-

ties of burns always must be considered and guarded against.

The therapeutic measures just discussed in reference to arthritis, particularly massage and heat, are of equal value in those painful conditions which are so frequently associated with arthritis, but which may occur without any accompanying joint involvement, namely, myositis and fibrositis. These conditions are ill defined; they are regarded as part of the rheumatoid state, their causation is not clear, nor is their course and natural history definitely established. Their outstanding symptom is pain, frequently associated with a considerable amount of muscular disability. These conditions are notoriously refractory to drug therapy, but their response to suitable physical therapy is often good.

Physiologic rest in chronic arthritis may be induced by the following positions:<sup>2</sup>

**Supine Position**—This position is to be assumed  $\frac{1}{2}$  hour after meals. The patient lies on a flat, firm mattress or on the floor if the mattress sags. The pillow under the head is eliminated, the arms are placed at right angles from the body, with hands resting on the mattress in a medial position, and the chin is drawn in. A thin pillow or roll under the scapulas forces the chest high, and a thin pillow or roll under the head of the tibia creates slight flexion of the knees and prevents strain on the lower portion of the back. A support is necessary at the feet to prevent foot-drop. Sandbags may be necessary to prevent rotation of the hips.

This position should be approximated as nearly as possible. The patient who has been long bedridden and has had several pillows under the head, producing flexion of the cervical portion of the spine and a flat chest, must be gradually adjusted to this hyperextended position, first by the gradual removal of the pil-

lows under the head and eventually by adding the roll under the scapulas. If the articular limitation prevents the prescribed position of the arms, approximate the position as nearly as possible, making an effort to obtain outward rotation of the head of the humerus to force expansion of the chest.

**Prone Position**—This position relieves the bedridden patient and may be adopted during a half hour of the rest period. A pillow is placed under the chest, and the arms are placed at right angles to the body, with the elbows flexed and resting on the mattress. A pillow under the lower leg assists in maintaining slight flexion of the knee and prevents a drop-foot position. Sandbags may be necessary to prevent rotation of the hips.

**Positions in Bed—*Recumbent Position***—This position serves to prevent deformity and to improve general circulation. The following instructions should be observed:

Make the mattress flat. Boards as a rule should be put under the mattress.

Preferably eliminate a pillow under the head. A flat chest and slowing up of the circulation result if a pillow is used.

Place a small pillow or roll under the head of the tibia. Subluxation of the knee frequently results from a pillow under the thigh.

Train the patient to lie with his elbows and wrists extended to prevent flexion deformities. The arthritic patient frequently assumes a position in which he flexes elbows and wrists and rests them on his chest for comfort and body warmth. The pressure of the arms on the chest retards full inspiration and slows up circulation.

Prevent outward and inward rotation deformity of hips by propping the legs in position with pillows or sandbags.

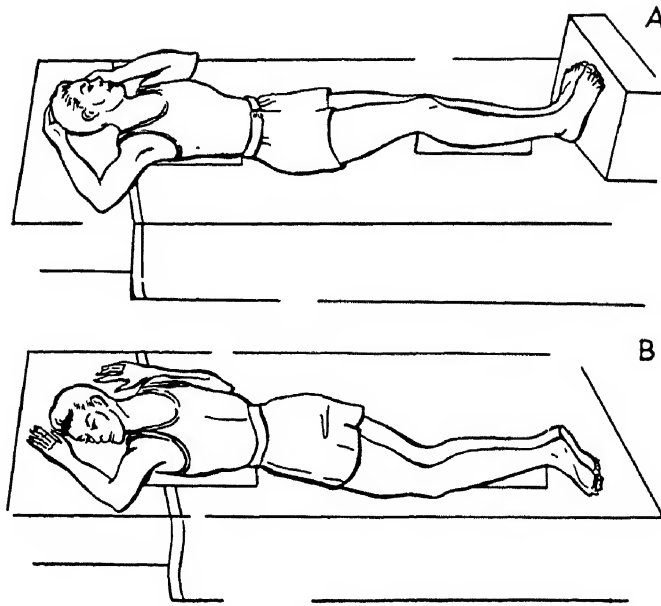


Fig. 1—Positions assumed in bed by the arthritic patient to obtain physiologic rest. *A*, the supine position. *B*, the prone position. (Manual of Occupational Therapy, 1943.)

Maintain a  $90^\circ$  angle of the ankles and prevent foot-drop by using a heavy box or bricks at the foot of the bed to hold the feet at right angle and prevent pressure of the bed clothes.

**Sitting Position**—Use a flat canvas or board back rest if possible. If a pillow is used it should be firm and extend from

the hips to the shoulders. The chin should be in, the head back, and the chest high. A firm pillow or roll under the head of the tibia to flex the hip and knee will prevent the patient from slipping down in bed and assuming a poor position.

**Position in a Chair**—Whether a wheel chair or a regular chair is em-

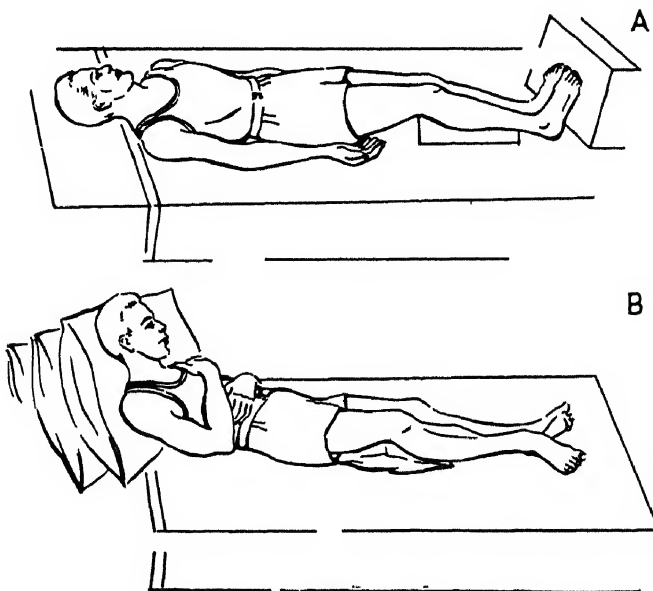


Fig. 2—The recumbent position assumed in bed by the arthritic patient to prevent deformity and to improve general circulation. *A*, good position. *B*, poor position. (Manual of Occupational Therapy, 1943.)

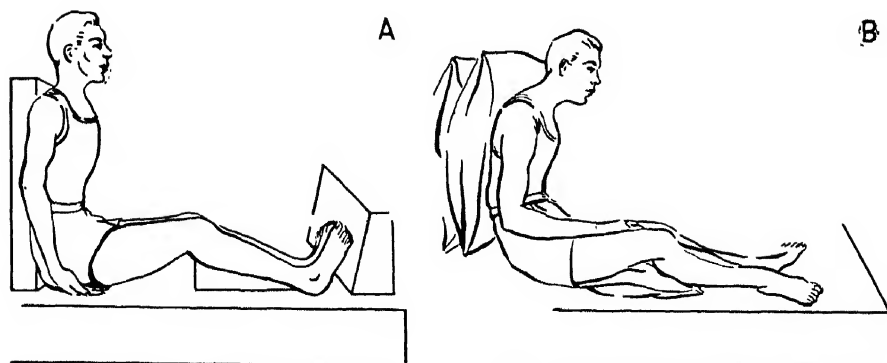


Fig. 3—The functional position assumed by the arthritic patient sitting up in bed for occupational therapy. *A*, good position. *B*, poor position. (Manual of Occupational Therapy, 1943.)

ployed, it should have a straight back. While sitting up the patient should be erect with chin in and chest high. If a pillow is used, it should be below the shoulders, so the head is not pushed forward and the chest flattened.

**Guide in Selection of Posture Chairs**—Support at the scapulas is essential. There should be a space between the top of the chair and the seat, so that the patient sits back in the chair. Slats, as shown in the illustration of bad seating (Fig. 4), press against the pelvis, causing rotation and poor posture.

### BACKACHE

The Flexion Treatment for Low-Back Pain, outlined by Breck and Basom,<sup>3</sup> varies somewhat according to whether

the backache is acute or chronic and whether it is severe or mild. The acute severe cases are best treated by putting the patient in a hospital bed with the back rest raised to 45° and the knee rest raised almost as far as it will go. If the patient is not in a hospital bed, he can be treated at home by means of a back rest and a knee support which place him in a position similar to that just described. This can be done easily and inexpensively by means of two boxlike supports, devised by the authors, which are made of ½-inch plywood. Pillows are placed over each of them. The back rest is triangular in shape in the side view and measures 18 inches on the two sides and 25 inches on the other. It is 22 inches wide, and the long side, where the patient's back rests,

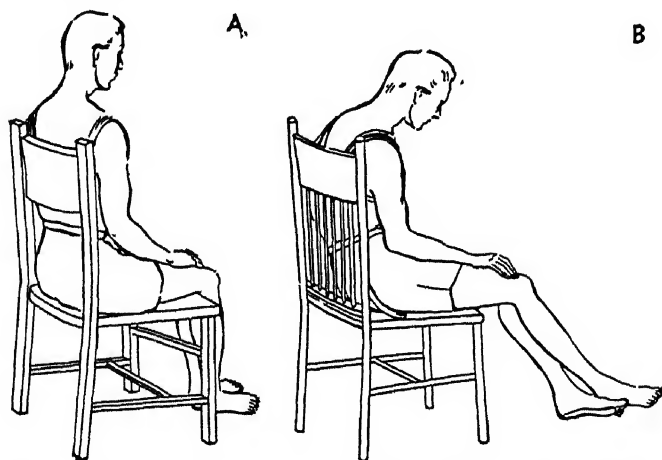


Fig. 4—The sitting position assumed in a suitable chair by the arthritic patient. *A*, good position in a well-selected chair. *B*, poor position in a badly selected chair. (Manual of Occupational Therapy, 1943.)



is made in two pieces, with the center depressed four inches in a hallowed-out manner, which makes the back rest much more comfortable.

The knee rest is a flat boxlike arrangement, with the two sides measuring seven inches high and 22 inches long. The patient is kept on his back, with the back rest and knee rest in place part of the time (usually two hours at a time, three or four times a day), and the rest of the time he lies on one side with his knees drawn up. He is advised never to lie flat on his face or flat on his back with his hips extended.

In addition to this, heat is used in the form of short-wave diathermy or a heat lamp. Massage is also given to help alleviate the pain and muscle spasm. The patient is given flexion exercises in bed the first day. The first exercise consists of pulling the knees up to the chest with the spine flexed, and the neck and chest brought well forward toward the knees. The patient is instructed to do this six times a day, starting with once each time and increasing until he is doing it ten times six times a day. The patient is usually much improved by the end of three to seven days, and can then be up and about. A few days after he can ordinarily return to work.

It is felt that the most important part of the treatment is to impress upon the patient the importance of flexing his lumbar spine and keeping it flexed.

In this summary the authors state that there is a sound basis for the flexion treatment of low backache due to a narrowed lumbar disc, regardless of whether the pain is due to a protruded disc, or subluxation of the lumbosacral, or lumbar facets.

Conservative flexion treatment, as outlined by these authors and utilizing their apparatus, has been found efficient for home treatment.

## DEFORMITIES OF THE THORACIC SPINE AS A CAUSE OF ANGINOID PAIN

It has been emphasized that measures which improved the posture of patients alleviated or abolished their discomfort. In this connection the work of Kerr is of some interest. He approached the treatment of angina pectoris from a unique standpoint, with the supposition that angina may be the result of myocardial anoxemia, enhanced by faulty refilling of the heart, and hence diminished oxygen supply to vulnerable tissues. Many of his patients had exhibited impairment of diaphragmatic motion, which he thought might further reduce the return flow of blood to the heart. Kerr applied abdominal belts to these patients, and sought improvement in posture. Many of his subjects improved under this régime. In the light of Smith and Kountz's experience,<sup>4</sup> it seems possible that the improvement he noted may have been due to the correction of general posture. Gallavardin stated that some cases of angina pectoris have a "collaring sensation," as of a portmanteau placed about the shoulders, radiating about the shoulder girdle. The attacks, he noted, were transient or of long duration, and might be provoked by movements of the upper extremities. He further stated that such episodes were usually indifferently relieved by nitrites. It is possible that Gallavardin may have been dealing with a problem similar to this.

Report has been made of 4 of 15 patients having anginoid pain attributable to spinal deformity. Frequently the seizures could be induced by movements involving the deranged spinal segments. Procedures applied in an effort to improve posture brought about improvement or cure of the symptoms.

The mechanism of the production of dorsal root irritation was considered in

the light of clinical findings, and an experimental study was made in order to investigate the problem further. This was done by using a cadaver, with spinal cord and nerves exposed, in which an abnormal degree of spinal flexion and extension could be produced. When the spine was either flexed or straightened to an abnormal degree, the spinal canal tended to become elongated so that the cord was drawn cephalad. This imposed tension on the spinal nerves, particularly at their angulation through the spinal foramina and at their attachments to the cord. It was postulated that movement imposed on the nerves under such tension may give rise to irritation of the fibers with the production of referred pain.

Some of these patients experienced unexplained transient relief from the use of nitrites. It is emphasized that this phenomenon, if ignored, might lead to an incorrect diagnosis of agina pectoris.

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## REHABILITATION

### Patients with Psychologically Protracted Convalescence

Dr. Bell,<sup>5</sup> Chief Medical Officer of the Workmen's Compensation Board, Ontario, asked his colleagues at the Compensation Board for their opinion as to what proportion of time lost following industrial injury is solely due to functional conditions.

The estimates he received ran from 15 to 25 per cent. In the year 1941, in the Province of Ontario alone, the man-day loss due to industrial injury was one and a quarter millions.

A complete answer to the question of etiology involves consideration of a great many factors, including those tendencies which contribute to produce a psychopathic personality.

The injury, as a rule, is of minor importance; at times, it would seem little more than an incident.

A great many medical men, in their eagerness to treat the injury, neglect to treat the patient. Their surgical skill may be beyond reproach, yet it never occurs to them to question subjective symptoms even well after anatomical recovery appears to be complete. Worse still, they unwittingly lend themselves to the production of a functional state by careless remarks in the presence of the patient and his friends. Many a patient with avulsed transverse processes has been told he has a fractured spine instead of a muscle injury, and, of course, there are always friends who can recall cases in which dire consequences followed such injuries, and some who may even know the amount of the pension received by so-and-so. To a patient, the word of his medical attendant is the voice of experience, and the confidence the doctor holds should be used for constructive purposes rather than sated in gloomy prognoses.

Now what is the answer to the problem? If the medical profession can be made to realize that it has a real live problem on its hands, an excellent start will have been made. Unfortunately, the attitude of many is that matters of psychology are outside the scope of the surgeon and something for the neurologist and psychiatrist to worry about. By the time the neurologist or the psychiatrist is sent for, the case is usually too difficult and complicated to permit of an easy solution. Furthermore, any surgeon or physician who thinks he can ignore psychology as an agent of healing is passing up one of the most potent forces at his disposal.

Solomon's<sup>6</sup> method of a psychiatric approach to rehabilitation is as follows:

**A. Understanding the Character or Personality of the Patient**—It is

possible for the physician untrained in psychiatry to gain sufficient skill in understanding the character of his patients, so as not to confuse a character trait with a symptom, not to be angered by the patient's aggressions, not to aggravate the patient's hostility, and not to foster dependent drives.

Because industrial patients have their physicians assigned to them, the usual patient-doctor relationship is not present. This requires that the physician be able to recognize personality types in order to gain their confidence and not be irritated by them. Examples of personality types frequently seen with psychologically protracted convalescences are:

1. Persons who are excessively defensive against being taken advantage of.

2. Persons with deep-seated feelings of insecurity.

3. Persons, most often women, who are excessively dependent.

4. Persons who since childhood have felt rejected.

5. Persons whose achievement motivation is dependent on the gratification of desires for praise and admiration from their superiors.

6. Persons with hysterical characters.

7. The martyr, "who sticks out his neck for trouble."

8. The hypochondriac personality.

9. The psychopathic personality, who is shiftless, dishonest, unreliable, undependable.

10. The person approaching senescence with a feeling of economic, occupational, and health insecurity.

The personality types emphasize the need for the adaptive management on the part of the physician.

**B. Evaluation of the Patient's Emotional Problems**—1. Problems related to the accident: Psychoneurotic reactions may appear when the patient has

been injured in an accident terrifying him.

2. Emotional problems collateral to the accident: Experience in industrial psychiatry indicates that the emotional reactions related to the accident, and to circumstances collateral to the accident, determine, in a given personality, the character of the protracted convalescence.

The accident may intervene while the patient is struggling to solve a bad marriage adjustment.

3. **Psychologic Problems in the Return to Employment**—When observations have determined that the convalescence has been psychologically protracted, the personnel director must carefully supervise the return to employment. He must recognize that the patient returns to work reluctantly for reasons already given.

4. **Recreation and Exercise Therapy**—While not infrequently it is possible to rehabilitate a patient from a psychologically protracted convalescence with psychotherapeutic interviews alone, the average patient will require additional therapy. Many of these patients are angry, they feel they have been "pushed around," their complaints have been challenged, their repeated requests for treatment have been met with repeated examinations, and for the most part society has not been too kind to them. At best, their behavior because of its conflictual nature and psychologic defenses leads to continued frustration. Their long period of relative inactivity and tension has usually left them weak and flabby, with bad hygienic habits and poor morale. Their philosophy of life was directed toward the establishment of a protracted disability instead of growth, health, and achievement. Solomon's experience shows that, because of the frustrations involved in such behavior, these patients will co-operate in a treatment which of-

fers them diversion, recreation, and play, good body development, and amiable companionship even if the acceptance of that treatment denies the further existence of the convalescence.

The patient should be introduced to the regimen with emphasis on play and recreation. As soon as he develops skill in a given sport, he should engage in competitive games. The patient should not be coerced into activity.

The physician should see the patient at his office for psychotherapeutic interviews, the purpose of which is to encourage the patient through friendly understanding, and, if possible, psychologic understanding, to engage in more and more activities. About six weeks is the average duration of treatment necessary to rehabilitate the patient.

The writer has been following Solomon's cases for some time and believes that he has a method that has prevented a permanent disability in many of these patients.

### **Treatment of the Injured Workman**

According to Griffiths,<sup>7</sup> the object of treatment is to effect a cure—that is, to obliterate altogether from the mind and body of the patient the effects of the injury sustained. Since in the human body repair does not occur without the formation of scar, 100 per cent anatomical and psychological recovery is not possible and some standard short of that perforce must be accepted. In the author's opinion, the best results can be obtained by accepting the restoration of full working capacity as the criterion of recovery.

Before we can set out to obtain this cure, we must determine what the workman has lost as a result of his injury and what we must restore. In a word: what is working capacity? It may be ability to stand, walk, run, jump, climb, pull, push, lift, turn, twist, manipulate; but, above all, to endure. Loss of any of these

attributes is the result of loss of power; therefore, whereas the criterion of recovery is restoration of working capacity, the goal of treatment is power.

Power is produced by muscle action, and in man muscle action is the only method of expression of power. Whether he be professional pugilist or poet, fighting, declaiming, dictating, or writing, the final medium of will or thought is muscular action.

None of the voluntary muscles works alone. Each works in a carefully balanced group; while one muscle contracts its antagonist elongates, just retaining sufficient tone to ensure that smooth and rhythmic movement shall be attained or that a static position against resistance shall be maintained with the minimum amount of effort. When a muscle contracts, its points of attachment tend to approximate, and that is only possible if the joint or joints crossed by the muscle or its tendons move.

Muscle power may be "... increased or conserved by the play of the tendons over fulcra produced by bony projections of fibrous tunnels. It follows, therefore, that if muscles are to act to the best mechanical advantage, anatomical reconstruction of bone and soft parts must be as perfect as possible; but efforts at this reconstruction must always be controlled by the consideration of muscle action. For example, in compound fractures associated with muscle damage, it may be necessary to aim at deliberate shortening of the bone in order to secure maximum power in the muscle. Joint movement *per se* is not only useless, it is most disabling—for example, a flail elbow. Joint movement caused and controlled by balanced muscle action is the very essence of power.

"Progress in treatment, therefore, is not indicated or estimated by attention to the angles of joints, but by the degree

and strength of the contraction of the muscles controlling the joints."

Thus, there must be such anatomical reconstruction of injured parts as permits the muscle to act to the best mechanical advantage; an adequate blood supply is equally important because it provides for adequate oxygenation, nutrition, and the elimination of waste, all essential in promoting repair and redevelopment. The blood supply depends not only upon the arterial flow but equally upon a good venous return. Unless the venous return is adequate, there is stagnation in the capillary circulation and a decreased blood supply with edema, the edema itself being of both the active and the passive types, leading to the matting together of tendons and muscles with fibrin and the ultimate formation of adhesions. A deficient venous return is the most important single factor in the causation of stiff joints following injury.

An increased blood supply to the part has been produced by various forms of heat, from blistering agents, through fomentations and radiant heat to diathermy. None of these methods, however, assists in the venous return. The venous circulation of the limbs owes little to the *vis a tergo* of the blood entering from the capillaries, but is mainly dependent on the contraction of muscles which act as pumping stations, forcing the blood centrally along the veins. The completely flaccid muscle does not assist in the venous return, but when the muscle is in a state of tonus the pumping action is functioning. It follows, therefore, that the process of healing in an injured limb can be assisted by keeping the muscles in a state of tonus, and hastened by keeping the muscles at exercise.

The aim of our efforts in treatment is the restoration of power through muscle-action, and to effect this power-reduction factors must be removed so that power-

production factors may operate. First, fear must be abolished. The workman's great fears are of pain, financial loss, unemployment, industrial de-grading, and litigation. At the Albert Dock Hospital steps are taken immediately after the patient's arrival to combat each of these five fears. The last four are eliminated by close co-operation between the hospital staff and the employers. All kinds of imaginary difficulties may be raised as to the successful working of this liaison, but after five years' experience it has been found that there are no insurmountable difficulties. The whole-hearted co-operation of the employers of labor in the interests of their workmen is invariably obtained. It is true that in obtaining this co-operation tact, understanding, and good will on both sides are necessary,

The aim of treatment is to restore power, not only to the injured part but to the whole body. The restoration of power can only be achieved by exercise, which in turn produces a flow of "more and better" blood and hastens tissue repair. But the flow of blood must be regular and not in fits and starts, so that exercise must be prolonged throughout the hours of the ordinary working day instead of for half an hour three times a week.

In order to make exercise possible without inducing fatigue, the exercises should be based upon established reflex action: At first the fundamental reflexes, then the conditioned reflexes, and finally impulsive action.

In the patient psychological effort must be reduced to a minimum because this effort produces fatigue at a stage much earlier than it would otherwise occur. Normality (*i. e.*, to use conditioned reflexes) must be encouraged. Normal working boots should be worn and sticks and crutches disallowed. Bad habits of grasp and grip and gait are prevented or

corrected by leading the patient back step by step up through his reflexes.

All this requires great psychological effort, but this effort must be made by the surgeon on behalf of his patients, and for him, like them, "getting fit is a whole-time job."

### **Rest and Exercise in Nerve and Tendon Injuries**

Koch<sup>8</sup> in these injuries believes that three considerations are of paramount importance:

1. One must secure healing of the operative wound by primary union or no good result can be accomplished.

2. The operation must be so carefully done that nerves and tendons heal with a minimum of inflammatory reaction and subsequent scar tissue formation.

3. The affected part must be kept at rest in such a position that there is a minimum of tension on sutured nerves and tendons until sound healing has taken place.

There are only two opportune moments for repairing divided nerves and tendons—immediately after the injury has occurred, and when the wound is soundly healed and induration and inflammatory reaction have disappeared from the surrounding tissues.

Tendons must not only heal soundly, but they must glide freely back and forth. The line of union must be so smooth and perfect that no excess of fibrous tissue develops to fix sutured tendons to the surrounding tissues. Nerves must be united with such fine silk, inserted only in the very outer sheath, that no fibrous tissue invades the nerve substance and prevents the downgrowth of nerve axons into the distal segment.

Mason and Allen's excellent experimental study has demonstrated clearly the process of repair in sutured tendons. By the end of five or six days, the tendon

ends are converted into a soft callus almost gelatinous in consistency. Any tension at this stage simply causes sutures to cut through tendon ends and pulls them apart. From the sixth to the sixteenth or eighteenth day, fibrous tissue resembling true tendon tissue gradually forms to replace the soft tendon callus. Movement during this period provokes excess of fibrous tissue formation and tends to produce the very adhesions to the surrounding tissues that the surgeon wishes to avoid. The most favorable results will be secured if the part is kept immobilized for 18 to 21 days in such a position that the affected muscles are relaxed as completely as possible. At the end of that period slight active movement is encouraged, but with maintenance of the position of relaxation for another week. At the end of four weeks active use is begun, but with care to protect the affected tendons from undue or sudden tension for another three weeks' period.

The same general plan of postoperative care can well be applied if only nerves have been repaired, but this important added consideration must be emphasized: After sutured nerves are soundly healed, the muscles supplied by the nerves in question must be kept supported and relaxed until regenerating nerve axons can make their way into the affected muscles. If paralyzed muscles are left unsupported and unprotected from the constant pull of powerful antagonists, they become hopelessly overstretched and the eventual return of function becomes an impossibility, no matter how carefully and accurately the nerves supplying them have been united.

### **Industrial Rehabilitation of Permanently Injured Workers**

According to Holmblad,<sup>9</sup> the success of rehabilitation really depends on the patient's "will to get well." If this is

lacking, the physician's task is much greater, because he has to develop it before he can show much in the way of results. In talking with patients and encouraging them in their progress, the author frequently develops the idea that there is a "real thrill" in getting well. When once they experience the gratification of improvement, steady progress is assured.

There are many inhibiting influences in a rehabilitative program that must be overcome. Holmblad has mentioned the early fears of the patient. Then there are fears of overcautious relatives or friends and sometimes of overcautious physicians or nurses. He has seen an overanxious employer disrupt a rehabilitative program by insisting that a plaster of Paris cast be applied to a fracture without displacement or by providing crutches when the attending surgeon wished the patient to use the foot or leg in walking—well-intentioned acts, but nevertheless interfering with recovery.

The job placement of handicapped workers opens up an excellent field for rehabilitation of the permanently injured or disabled person. The co-operative attitude of most employers in providing suitable work for their injured employees is most commendable and does a lot to rehabilitate these employees. Many of them are better employees after their experience.

The influence of the physicians and surgeons who head the medical departments of industries has been distinctly noticed in the job placement of handicapped workers during the last decade. Dr. Daniel Lynch, of Boston, by his persistent devotion to such placement, has rehabilitated many workers who were slated for early retirement because of disabling conditions. Patients with crippled hands are re-educated to do certain types of clerical and office work. Many

telephone operators threatened with retirement because of decreased hearing are rehabilitated and kept at work by a combination of amplification of the telephone receiver with a hearing aid device.

Since rehabilitation depends so much on the will of the patient to get well and on his attitude toward rehabilitation, the problem of treatment resolves itself into one of education and supervision. The physician must know exactly the cause and nature of the disability and what will be reasonable and safe rehabilitative measures. With this foundation, he proceeds to create an incentive for the patient to get well. Treatments ease pain; activity and use are encouraged to the maximum of the patient's tolerance; suggestions and encouragement are constantly provided.

It is not enough to convince the patient of his ability to get well; one must convince his relatives and friends. When the time is reached for the patient to go back to the plant or office, his employer, foreman, and fellow workers must not destroy the rehabilitation thus far achieved. In this connection it should be emphasized that such patients do not want sympathy or special consideration. It means a great deal to them to be able to carry on actively and to accomplish the same type of work as their fellow employees. They want to earn their wages as their associates do. They do not wish to be looked on as creatures of charity, sympathy, or especially privileged. They want to stand on their own feet, proud of their achievement.

### **Problems in Employing the Physically Handicapped**

In problems in employing the physically handicapped, Albee<sup>10</sup> says that the question remains the same: "Why should I hire half a man, if I can hire a whole man?" From an economic viewpoint, the



employer should never hire half a man if he can get a whole man. The question is: What is a whole man?

A cripple who has been trained for a job is bringing not a half-man's work, but a whole man's work to that particular job. Throughout the country, in every state, there are now rehabilitation departments, bureaus, or other agencies, whose main responsibility is to see that the cripple is prepared to fill some job in modern industry—not just any job, but a job for which his particular abilities, education, and background fit him in as close to a tailor-made fashion as modern medicine, psychology, and pedagogy can produce.

In addition, the cripple brings to a job a rare kind of loyalty—he appreciates being given a chance to prove he is not a social liability, but a self-respecting member of his community. He has a type of patience practically unknown among the able-bodied. If you had seen the years of pain and agony some of the rehabilitated cripples have endured that they might not spend their lives in bed or a wheel-chair, you would realize that the good old-fashioned “guts” required to rise above such suffering gives the cripple a plus that makes his hiring one of the wisest personnel moves some employers ever make.

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## EXERCISE IN ASTHMA

Hurst,<sup>11</sup> in discussing expiratory exercises for asthma, states that in an attack of asthma the obstruction caused by the spasm of the bronchioles is diminished by the rise in the negative pressure in the thorax caused by the forced inspiration and increased during the forced expiration by the conversion of the negative into a positive pressure. This explains why asthma differs from all other forms of dyspnea in being mainly expiratory. The respiratory excursion is much re-

duced and the child is unable to take exercise without dyspnea. This condition is often mistaken for emphysema, but in contrast with true emphysema it can be rapidly and completely cured by expiratory exercises, an excellent illustrated description of which has been edited by Dr. Livingstone for the Asthma Research Council. These exercises restore the normal postural tone of the thoracic muscles, so that the chest resumes its natural shape and the lungs their normal size, the respiratory excursion returns to normal, and the child is able to take vigorous exercise without distress. So long as any tendency to asthma persists, simple expiratory exercises should be carried out every morning and evening unless an attack is actually present, and any postural errors, especially habitual shrugging of the shoulders, should be corrected.

Expiratory exercises should not be regarded as a substitute for walking and open-air games but as a form of training. Nothing is more undesirable than prohibiting games. An asthmatic child should be taught to regard his asthma as an inconvenience and not a disease. It is almost always possible to find a school where he is free enough from attacks to be able to join in every kind of sport. Swimming is particularly beneficial. In peacetime, whenever possible, the Christmas holidays should be devoted to winter sports and especially skiing. If exercise is found to cause shortness of breath, this can be often prevented by taking a small dose of *ephedrine* or *theophylline* half an hour earlier. Asthmatic children should be encouraged to have a cold bath every morning all the year round or at least a cold douche after a hot bath of short duration. Bed is the worst place for an asthmatic in the daytime unless bronchitis is present, and even after a disturbed night it is best to have a cold bath and get up for breakfast, if

necessary, after a preliminary dose of ephedrine or theophylline.

Hurst believes that every asthmatic can derive much benefit from good advice. He can be taught a way of life, and, among other things, how to avoid the exciting causes of his particular brand of asthma, how to control attacks which he is unable to prevent, and above all how to be happy in spite of the bad luck of having been born with the asthma disease.

### ACUTE POLIOMYELITIS

The most important difference between the Kenney and the orthodox methods of treating poliomyelitis, according to Key,<sup>12</sup> is that in the Kenney method emphasis is placed upon muscle spasm as the most important feature of the disease and efforts are made to relieve this spasm by hot fomentations, while in the orthodox method flaccid paralysis of muscles is considered the most important feature of the disease and efforts are made to protect and restore function to the paralyzed muscles. The other two symptoms which are stressed by Miss Kenny (incoordination and mental alienation) are recognized under different names, but are treated in much the same manner under each method. However, it is believed that early active exercise of muscles is harmful and tends to prolong the stage of tenderness and contracture, and muscle training is not begun until these symptoms have subsided, while Miss Kenny begins her muscle training as soon as possible after the diagnosis of poliomyelitis is made. Splints are also considered a useful adjunct to treatment where they are indicated.

The symptoms which Miss Kenny calls muscle spasm are recognized and treated in the ordinary method, but they are called rigidity and muscle contracture, and are treated by immobilization in splints or casts to relieve the pain and

prevent contractures and the development of deformities. In anticipation of the criticism that even though orthodox treatment has recognized the so-called muscle spasm it has failed to emphasize and treat this symptom, the author wishes to state that rest is probably the most important therapeutic measure in our armamentarium and that in order to put a muscle at rest we immobilize the part. Consequently, we treat the tender, painful contracting muscles by rest. This is obtained by splints or casts. The reason these symptoms have not been emphasized is that they tend to subside when the limb is put at rest. The tendency of the muscles to contract (so-called muscle spasm) subsides when the pain and tenderness disappear, and if deformities are prevented this symptom is rarely an important problem under orthodox treatment. It has not been emphasized because it subsides spontaneously.

### ULTRAVIOLET RADIATION

**Acne**—The Council on Physical Therapy<sup>13</sup> states that acne vulgaris is divided into a number of clinical varieties. The intelligent management of the disease requires a clinical knowledge of the various types because the therapeutic indications differ somewhat with the type. Acne indurata is the common type. It is encountered mostly in late adolescent and early adult life and is chronic in course and appearances. In addition to comedones, pustulous follicular orifices, and scars, there are numerous large, deep-seated pustules, and perhaps occasional indolent cystlike lesions. The skin is likely to be excessively oily. This type usually tolerates and responds well to vigorous treatment.

The more acute types—acne pustulosa and acne erythematosa—are more likely to be associated with detectable and correctable systemic disturbances. It is ad-

visible to begin treatment with soothing topical remedies before physical therapy.

Comedones and acne papulosa are seen most often at puberty. The lesions consist of blackheads and papules, and there may be also some pustules and an oily skin. At times these types disappear spontaneously or yield quickly to stimulating topical remedies. Not infrequently, however, it is impossible to cure the puberty cases permanently until the patient is somewhat older. It is possible, as a rule, to control the disorder through this period with suitable topical remedies or with ultraviolet radiation or both. It is important to do so; otherwise acne indurata, oily seborrhea, scars, and a coarse skin are apt to develop.

Although ultraviolet radiation has been blamed for superfluous hair in cases of acne vulgaris, it is generally agreed that this agent cannot make hair grow on glabrous skin. Hypertrichosis in association with acne vulgaris has been noted in the absence of local treatment of any kind. However, when girls or women have a tendency to grow hair on the face, it is theoretically possible that the frequent application of remedies producing hyperemia might encourage the growth.

**Acne Varioliformis**—Ultraviolet radiation is of doubtful value.

**Furunculosis and Carbunculosis**—Many physicians believe that an erythema or a blistering dose of ultraviolet radiation, preferably with a water-cooled lamp with compression, when applied to a boil in the very early stage of evolution, will either abort the lesion or greatly modify further development. In the hands of most dermatologists this procedure has been uncertain and disappointing. Recurrent boils indicate some constitutional fault—organic, functional, or immunologic—which must be corrected if possible. In such instances, it is possible that a long course of general

body irradiation, using either the sun or an artificial source of light, might prove beneficial. While the general impression is that such treatment is helpful, there is no conclusive evidence that this is so.

**Neurodermatitis**—The disseminate type of neurodermatitis, when severe, is one of the most recalcitrant and distressing of the dermatoses. It occurs for the most part in patients who give a personal or family history of allergic disorders—urticaria, hay fever, asthma—and the patient is often sensitized to a large number of substances—food proteins, epithelial products (hair, dander, feathers), pollens, and bacterial proteins. The neurogenic factor is prominent, and there may be endocrine dysfunction. The disease is common in infants, children, and adolescents, less common in young adults and uncommon in older persons. There are acute exacerbations and remissions, both of which may be of short or long duration. Itching is likely to be almost intolerable.

There is a difference of opinion regarding the efficacy of ultraviolet radiation (general body irradiation) in neurodermatitis. Certainly many patients improve when they are able to indulge in heliotherapy, but it has been impossible thus far to determine whether the improvement is due to a combination of environmental factors (rest, relaxation, contentment, salt-water bathing, effect of moving air on the naked skin, change of climate, escape from causative proteins) or to ultraviolet radiation.

Only occasional good results are obtained with artificial ultraviolet radiation, and in these instances improvement might have been due to other factors. Many patients have a low tolerance for radiant heat and appear to be made worse with small doses of ultraviolet radiation. Amounts sufficient for erythema are likely to precipitate an exacerbation.

### Ultraviolet Lamps for Disinfecting Purposes

Clinical evidence submitted to the Council on Physical Therapy<sup>14</sup> shows that under properly controlled conditions the killing of air-borne micro-organisms by ultraviolet rays may be used to supplement other methods of disinfecting air for prevention of cross infection in contagious wards, in nurseries, and for reducing air-borne infection of wounds in hospital operating rooms. Council acceptance is limited to ultraviolet disinfecting lamps, designed for installation in hospital nurseries, hospital wards, and operating rooms.

Satisfactory evidence is not available to warrant acceptance of ultraviolet lamps for disinfecting solids. In view of the present available evidence, ultraviolet radiation appears to be an uncertain means of sterilizing solid objects (drinking cups, combs, brushes, shaving utensils, toilet seats, and shoes), even if irradiation of the whole surface is possible. Ultraviolet lamps for disinfecting purposes are not accepted for disinfecting air in schools, waiting rooms, public gathering places, and large halls. The evidence now available does not indicate that the incidence of colds can be reduced by the installation of ultraviolet lamps and by the irradiation of an occupied enclosure.

It is noted that a lamp used for disinfecting purposes is a single unit in an installation, and that compliance of the ultraviolet output of a single lamp unit with the Council's requirements does not insure adequate radiant disinfection or the safety of the occupants of the room in which an installation of such lamps is in actual use.

The total amount of direct and scattered ultraviolet radiation incident on the occupants must be kept below the level that will produce conjunctivitis, erythema, and any other (at present un-

foreseen) injurious physiologic effects that may arise from prolonged irradiation. This requirement may be met by suitable arrangements of the lamp fixtures and baffles and not by requiring the applicants to wear glasses and special covering of exposed parts of the body (face, hands) normally uncovered. Hence, if the irradiation is of penetrating intensity, in a corridor of the hospital for example, care should be taken that the attendants do not receive an exposure which will cause injury to the skin or eyes, and particular attention should be taken to make sure that the intensity of the space at eye level through which a transient may pass or tarry momentarily will not cause injury to the eyes. Under no circumstances should the occupants of a room be able to look directly at the burner when standing within the region of potent intensity.

Ultraviolet lamps for disinfecting purposes shall have, under suitable ventilating conditions of a room, a concentration of ozone not to exceed one part in 10,000,000.

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# RADIOLOGY

*Edited by* EUGENE P. PENDERGRASS, M.D.

## ROENTGEN DIAGNOSIS

ROBERT P. BARDEN, M.D.

### Technic

**Stereoscopy**—It is the common practice in stereoscopic radiography to shift the tube a distance equivalent to the average human interpupillary distance (2.5 inches) in examinations made with the tube 36 inches from the film. However, the principle of stereoscopy in radiography is different from that in photography because the roentgenograms show shadows of objects some distance from the film, and when the roentgen tube is shifted 2.5 inches, these shadows are displaced much more than a flat plane would be, as in a photograph. If the distance between the shadows on x-ray films due to shift of the tube between exposures is greater than three-eighths of an inch, the average person cannot fuse the resulting shadows to see depth. It is therefore necessary to shift the tube much less between exposures than is ordinarily done in order to obtain images which are easily fused when the roentgenograms are viewed. The actual amount of the tube shift should vary depending on the distance of the object from the film and the tube-film distance, according to the equation:

$\frac{3}{8}$  inch : most distant point of object from film ::  
x (tube shift) : anode to nearest point of object

It would appear important that this theoretical suggestion be sufficiently tested in practice to determine whether better stereoscopic roentgenograms can be obtained than are now available.<sup>1</sup>

**Foreign Bodies in Eye**—There has recently been described a simple method for localizing an opaque foreign body within the eye, which does not require any of the complicated apparatus of the commonly used Sweet localizer. The

new method is based on the principle of rendering the image of the patient's eye opaque on the film by substituting an artificial eye in the position of the real one and making a double roentgen ray exposure. The apparatus consists of a metal base which can be fastened securely to the top of a radiographic table and which supports a mast holding a movable pointer. An artificial eye fits into the end of the pointer so that its corneal surface is always 1 mm. from the tip of the pointer. This artificial eye is made of wood encompassed by wire meridians, and contains an opaque lens.

When localization of a foreign body is necessary, the patient lies prone on the table top with his head immobilized, and his chin on a cotton pillow. His eyes look straight ahead and the pointer of the apparatus is brought to within 1 mm. of the cornea. Stereoscopic films are obtained, after which the patient is removed and the artificial eye inserted in the pointer. A second flash exposure is then made on each of the stereoscopic films with the tube in the proper positions. The resulting films show the opaque foreign body within the shadow of the artificial eye and its exact position can be determined by relating it to the meridians and the equator and the semiopaque lens. There is no doubt that the simplicity, speed, and potential accuracy of this method will make it exceedingly valuable in many hospitals and offices where elaborate apparatus is not available, and that in military medicine, this ingenious aid may well be responsible for saving the eyes of many patients.<sup>2</sup>

**Nonopaque Foreign Bodies in Soft Tissues**—Recent research in industrial roentgenology has shown that better definition of the image of a small object with

the same or nearly the same density as the substance in which it is embedded can be obtained if the main body of material is immersed in a liquid of the same density as its own. This serves to produce a more uniform background against which a faint difference in density of the foreign body will be more apparent. This is of practical importance in medicine where it is suspected that pieces of glass, thorns, etc., are present in tissues and cannot be identified by ordinary roentgenographic methods, or in the demonstration of very faintly calcified gallstones or renal stones. The part to be studied is immersed in water or placed in a cast of paste made of a material of density similar to body tissues. It is important that such a cast have parallel edges to obviate the normal differences in density due to the rounded contours of the part being examined. In addition a low voltage, long distance technic is recommended.<sup>3</sup>

### Head

**Brain Tumors** — Although displacement of the calcified pineal has long been known as a valuable localizing sign of intracranial mass lesions, it is well to be aware of the occasional case with a "paradoxical" shift. Three cases of posterior fossa tumor have been reported in which the pineal was displaced posteriorly to a significant degree, which might have caused an erroneous surgical approach to be made, if sole reliance had been placed on this sign. Pneumoencephalography in these cases will show an internal hydrocephalus due to pressure of the posterior fossa tumor on the aqueduct. The enlarged third ventricle is responsible for pushing the pineal posteriorly.<sup>4</sup>

### Heart

**Patent Ductus Arteriosus** — The first successful ligation of a patent duc-

tus arteriosus was performed by Gross in 1938. A late article reports 50 cases, proven by operation, with three post-operative deaths. These results indicate the need for an accurate diagnosis, because a successful operation results in a dramatic change in a patient from hopeless invalidism to full health. The chief signs by physical diagnosis are a machinery murmur and a palpable thrill.

Because of the presence of this arterial shunt between the aorta and the left pulmonary artery, the following functional changes occur: The left ventricle enlarges because of greatly increased output of blood; more blood through the left ventricle and pulmonary artery results in increased pulsation; the left pulmonary artery enlarges, since it receives blood from both the right ventricle and the aorta; greater pulsations are present in the vascular subdivisions in the lungs, and there is vascular congestion in the lungs because of the increased volume of blood in the lesser circulation, with resulting enlargement of the left auricle, if the mitral valve is not large enough to transmit all the blood it receives.

In the roentgen examination of this condition, fluoroscopy plays the most important rôle. The diagnosis is strongly suggested if most of these signs are present: (1) An enlarged left ventricle; (2) dilated pulmonary artery; (3) enlarged left auricle; (4) engorgement of pulmonary vessels; (5) exaggerated pulsation of the left ventricle and pulmonary artery and its subdivisions, known as "hilar dance."<sup>5</sup>

Angiocardiography is also extremely useful in contributing to the diagnosis. After rapid intravenous injection of 70 per cent diodrast, films will show a distinct localized dilation of the descending aorta just below the isthmus which varies in size and shape from a localized bulge to a uniformly dilated segment. This

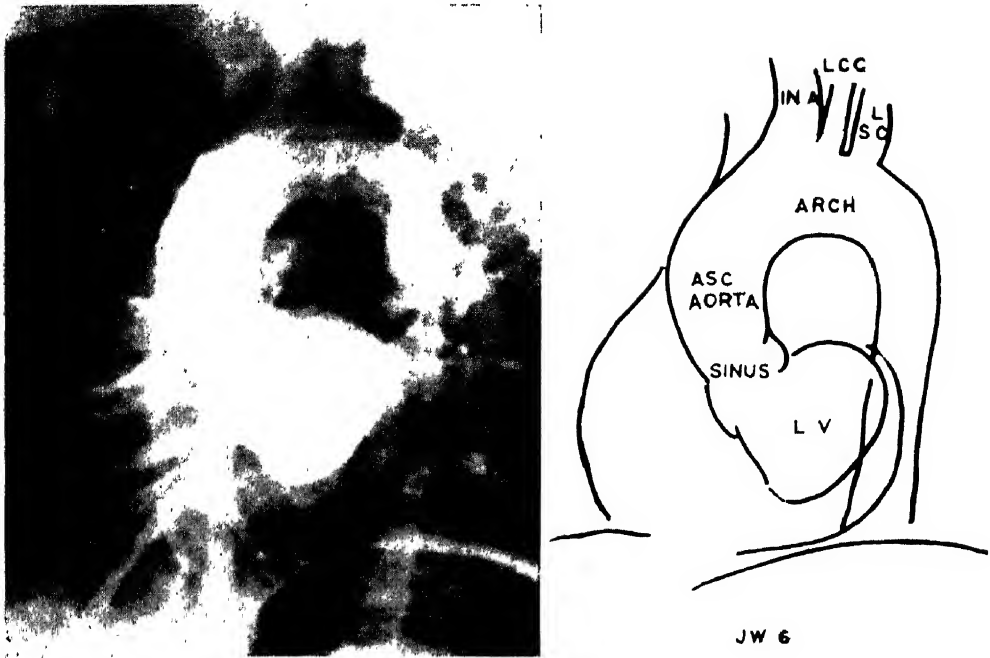


Fig. 1.—Normal boy, age 14. Left anterior oblique position. The aorta shows a normal smooth curve. The lumen is uniform in the arch and proximal descendens. (M. F. Steinberg, A. Grishman, and M. L. Sussman: *Am. J. Roentgenol.*)

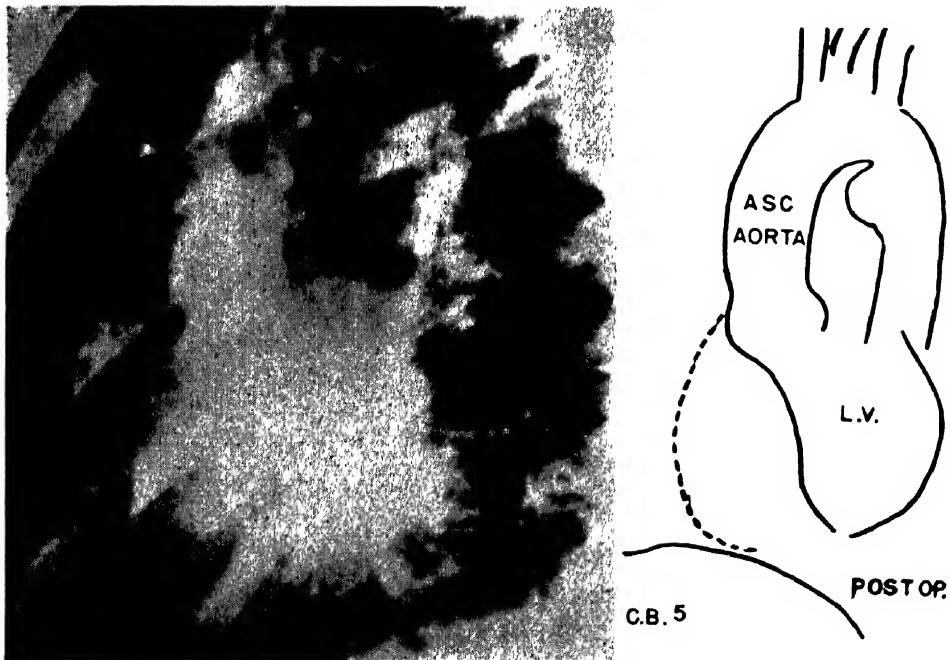


Fig. 2.—Female, aged 21. Patent ductus arteriosus (operated). Postoperative angiogram showing aneurysmal dilation of the proximal descending aorta. This probably represents a traction aneurysm of the aorta. Preoperatively, angiogram showed a more diffuse dilation. (M. F. Steinberg, A. Grishman, and M. L. Sussman: *Am. J. Roentgenol.*)



appearance is due to the infundibulum of the ductus or a traction aneurysm of the aorta. The actual ductus is so short and overlain by so many other shadows that it cannot be visualized. Another constant finding is an elevation of the main and left pulmonary arteries, as if they were being drawn toward the aortic arch, and three-quarters of the cases will show dilation of the pulmonary artery, and varying degrees of left ventricular hypertrophy. Of 27 cases studied by angiocardiology, 26 showed the characteristic changes described above, with the localized aortic bulge being the most striking finding.

It is evident that much skill and care is necessary to separate the cases of patent ductus alone from those with other congenital cardiac lesions, but the great service done the patient when an accurate diagnosis leads to a successful operation should present a constant incentive for the discovery of more patients with this curable disease.<sup>6</sup>

### Lungs

#### The Posteromedial Pleural Line—

This is the name given to the slender marginal line of demarcation just to the left of the lower thoracic spine in the anteroposterior film of the chest. This shadow is caused by the mediastinal pleura seen on edge against a background of air-containing lung. It may be absent on the left, and is usually absent on the right because insufficient portions of the pleura lie in a plane parallel to the central roentgen beam.<sup>7</sup>

When present, this shadow has diagnostic significance. Since it hugs the lateral border of the vertebrae, it reflects early swellings about them. The posteromedial pleural line may show a localized bulge, or loss of its sharp character as a result of paravertebral hematoma following injuries, cold abscess, anything caus-

ing collapse and increased diameter of the dorsal vertebrae, such as fractures and tumors, pyogenic abscess, and osteochondritis. A deliberate attempt to identify and trace this pleural shadow on films of the dorsal spine and chest may well result in the earlier diagnosis of many lesions included in the list above.<sup>8</sup>

**Postthoracoplasty Roentgenograms**—The manner in which the ribs regenerate after thoracoplasty operations often reflects the condition of the soft tissues lying beneath them. When the space enclosed by the rib fragments contains an unclosed cavity or aerated lung, the regenerating ribs take the shape of a localized lateral convexity because the increased pressure in the cavity or aerated lung prevents the new-formed bone from assuming a flat contour. Of 78 patients with a positive sputum following thoracoplasty, 63 were found to have this localized bulge on roentgenographic examination, while in no case was it found in 75 patients with negative sputum after operation. Other, less frequent causes of a residual localized lateral convexity are loss of periosteum locally, residual fluid in the pleural cavity, and bronchopleural fistula.

In placing the patient in position for the postthoracoplasty roentgenogram, it is important that the operated side of the chest be placed at a slight distance from the film while the unoperated side of the chest is pressed firmly against the film holder. Following operation, the contour of the chest changes, and it is only by placing the patient in this 5 to 10 degree oblique position that a true silhouette of the lateral chest can be obtained, and it is in this true silhouette that the presence of a localized bulge will be shown most clearly. In addition, if the patient's head is inclined away from the operated side, it will obviate some of the thoracic scoli-

osis which is another sequel to the operation.<sup>9</sup>

**Silicatosis**—While there is a voluminous literature on the lung changes caused by the inhalation of finely divided pure silica, combined silicas (silicates), with the exception of asbestos, have not been thought to produce pneumoconiosis. However, claims of incapacitating pulmonary fibrosis in talc workers led to further investigation of this possibility, particularly since there had been scattered clinical reports of nodulation occurring in the lungs of persons exposed to silicate dust for long periods of time.

Talc is obtained from tremolite deposits which are mined with very little hard rock drilling and samples of dust from mines and mills showed absence of free silica. The drillers in the mines work in dry dust but are supposed to wear respirators. In the mills the main dust exposure occurs at the operation of bagging. Of 227 men examined, 28 showed some changes in chest roentgenograms, and 18 of these showed marked pulmonary fibrosis with accompanying dyspnea. Of these with definite lung changes, 14 also showed calcified pleural plaques which were often limited to the diaphragmatic surfaces of the pleura and were apparently not, in themselves, producing symptoms either present or past. More of the men with advanced disease had worked at the bagging operation in the mill than at any other type of job.

The earliest change seen on the films was a "ground-glass" appearance of the lungs, and like the findings in asbestosis, the patient's disability was often more severe than would be suspected from the appearance of the roentgenogram. That changes in the lungs resemble those seen in asbestosis might be suspected since talc dust exists as fiberlike crystals similar to asbestos crystals. The explanation of the calcified plaque is more diffi-

cult. The size of the talc crystals prevents their reaching the hilum and indicates that their effect will be mainly in the lung periphery. It is possible that the calcification may be secondary to a sterile inflammation set up by the sharp crystals but no similar calcification occurs in the closely related disease of asbestosis.<sup>10</sup>

### Gastrointestinal Tract

**Respiratory Function**—It is known that during fetal life there is no air in the stomach, but that air appears in the gastrointestinal tract with the infant's first breath. In forensic medicine, the demonstration of such air on roentgenograms is the most delicate test of the fact that the infant was alive at birth. The mechanism of the entrance of this air is uncertain and its fate unknown. It has long been thought that the air was swallowed during crying, but against the concept of aerophagia are the following points: Strong esophageal peristalsis is necessary to force air into the stomach and this does not occur in the normal infant esophagus; something must be swallowed along with the air, either food or saliva, which does not occur during crying; at least two infants have been studied in which the gas bubble in the stomach was smaller after feeding barium than it was before. An alternative explanation of the presence of air in the stomach is that it is sucked in during inspiration because of the negative pressure which occurs in the esophagus.

The regulation of the amount of air entering the stomach is a function of the diaphragm about the hiatal opening. The same thing occurs during eating, when food (or barium) is held up at the diaphragm during inspiration and passes on into the stomach during expiration. This phenomenon is commonly observed during fluoroscopy of the swallowing act.

Disturbances in diaphragmatic function lead to changes in the air content of the stomach, and an excessively large air bubble in the stomach is one of the most certain sequels to paralysis of the diaphragm. When the function of the diaphragm is restored in these patients, the amount of air in the stomach immediately decreases.

Evidence that air can be sucked into the stomach is seen during gastroscopy where the organ expands with each inspiration of the patient; furthermore, in cases of congenital atresia of the esophagus, if the lower end of the esophagus is connected to the trachea, air appears in the digestive tract without the possibility of swallowing, and, finally, ventriloquists and postlaryngectomy patients talk by filling their stomachs with air as a result of a preliminary deep inspiration. As final proof of the concept of respiration occurring in the gastrointestinal tract, there may be cited the cases of two infants living 5 and 25 hours after birth with audible crying who were found at autopsy to have complete atelectasis of both lungs which had never contained air. "Digestive respiration" in the newborn is probably a regular subsidiary of pulmonary respiration at least during the first week of life. It is interesting that such digestive respiration also is known to occur in some fishes, particularly those equipped with a "swimming bladder."<sup>11</sup>

**Pyloric Stenosis**—In adults with vomiting and evidence of obstruction to gastric emptying it is often difficult to determine whether pyloric stenosis is due to organic thickening and narrowing of the wall, or to edema and spasm which may prove reversible under proper treatment. The differentiation of these two conditions usually requires several weeks of gastric lavage and small feedings followed by another roentgen study. By close attention to a new sign, however,

it may be possible to determine at the first examination whether the obstruction at the gastric outlet is organic or functional.

It is evident that with any long-standing obstruction, hypertrophy of the wall of the stomach will ensue. Since organic disease of an infiltrative nature will usually have been present for a much shorter time than the edema or spasm present about benign chronic ulcers, for instance, it follows that differentiation between the two conditions can be made if hypertrophy of the gastric muscle can be demonstrated. If the stomach retains some of its tone it is possible to show the gastric wall radiographically by examining the patient in the supine right oblique position and using careful palpation. Under these circumstances, the stomach wall will appear as a negative shadow with barium on one side and the thin line of the serosa on the other, highlighted if the transverse colon contains gas. On Bucky films made with reduced kilovoltage this shadow should be seen at some point along the distal two-thirds of the greater curvature, and if it measures more than 4 to 5 mm., hypertrophy of the wall is present.<sup>12</sup>

**Leiomyosarcoma of Stomach**—This tumor is the most common, submucous, intragastric growth and is usually highly malignant. It may arise as a single or multiple lesion, with no symptoms for a long time until the sudden appearance of numerous metastases (especially in lungs) or severe secondary anemia or hematemesis. Often the roentgen appearance is that of a tiny filling defect in the stomach with a tiny ulceration. As would be expected from its position within the stomach wall, the tumor may grow toward the mucosal or serosal surfaces and the latter may become very bulky before being recognized. The chief roentgen characteristics are a sharply

outlined filling defect, possibly showing a central ulcer, with no disturbance of surrounding mucosa or alteration in peristalsis.<sup>13</sup>

**Ileocecal Valve**—The ileocecal valve is composed of two lips bounding a slit-like opening between the small and large intestine. On their adjacent aspects these lips have mucosa and muscle from the ileum and on the side away from the

patient showed edema of the valve associated with thickening of the terminal ileum and a pathologic diagnosis of regional enteritis. A review of other pathologic specimens showed that thickening of the ileocecal valve is a common finding in regional enteritis, even in its early stages. It is evident, therefore, that by close attention to the ileocecal region during barium enema examina-

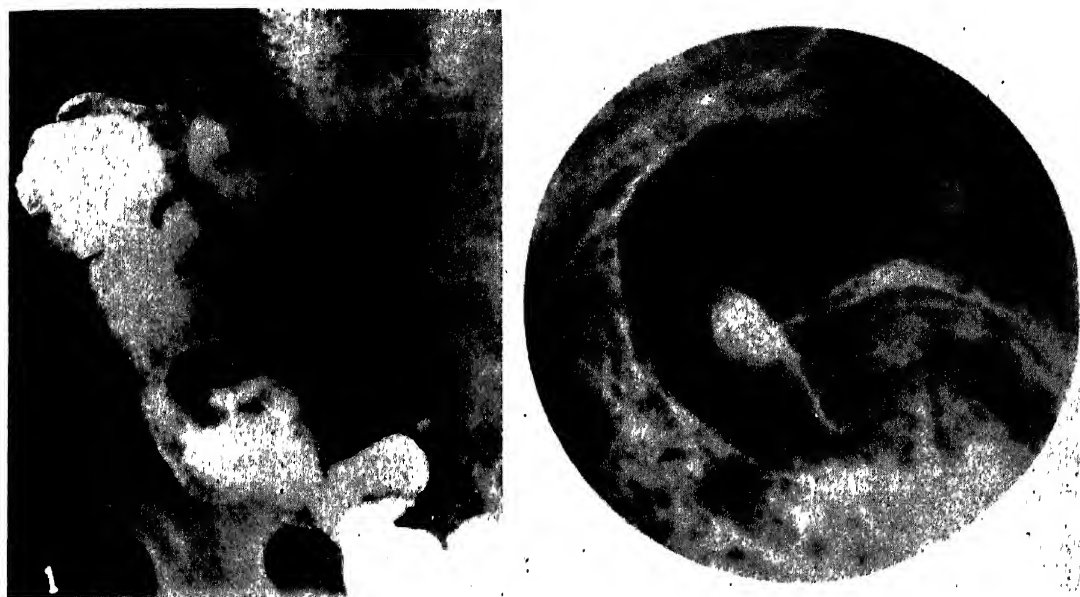


Fig. 3.—Enlargement of the ileocecal valve. Hypertrophy and edema of the ileocecal valve. A, roentgenogram taken without pressure, after ingestion of barium, shows a large defect about the ileocecal junction, interpreted originally as suggesting slight intussusception. B, roentgenogram taken with pressure shows the defect about the ileocecal valve with the terminal ileum passing through its center. This is reproduced somewhat larger than A. Operation showed these changes to be due to edema. (R. Golden: *Am. J. Roentgenol.*)

opening, mucosa and muscle from the colon. The normal lips of the valve protrude slightly into the cecum and can sometimes be recognized on pressure films of the cecum made during fluoroscopy of a barium enema. Recently, two cases have been described showing enlargement of the lips of the valve, diagnosed by roentgen examination and proven by operation. One of these patients, a chronic alcoholic, was found to have marked edema of the mucosa covering the lips of the valve with hypertrophy of the muscular layer. The other

tions, cases of hypertrophied valves may be discovered which should suggest the need for further study of the small intestines.<sup>14</sup>

**Pancreas**—Cystic fibrosis of the pancreas is found in 3 per cent of autopsies performed on infants and young children. On the other hand, the clinical diagnosis of this condition is rarely made, probably because the associated lung findings overshadow the lesion in the pancreas.

Pathologically, this condition is a congenital, familial steatorrhea with fibrosis

of the pancreas and bronchiectasis. It is thought that the degeneration of the pancreas is due to abnormal secretion which inspissates in the ducts and causes atrophy secondary to back pressure. The changes in the bronchial tree are supposed to result from epithelial metaplasia due to vitamin A deficiency. In 35 cases the average age of onset was two months and the average age at death, eight months. A definite familial susceptibility exists.

Inasmuch as this disease is found relatively frequently at postmortem, there must be many other cases living with less severe pancreatic damage. A proper clinical diagnosis may result in life-saving measures in the form of substitution therapy of pancreatic preparations. The diagnosis may be suggested by assaying the duodenal juices and finding an absence of pancreatic trypsin and lipase. Roentgen examination of chest and abdomen will reveal abnormalities which should conjure up the diagnosis when evaluated with the history and physical findings. The commonest roentgen signs are: (1) Subacute or chronic bronchitis or bronchiectasis affecting the upper lobes as much as the lower; (2) marked chronicity of the chest findings which are therefore often mistaken for tuberculosis; (3) frequent areas of atelectasis from bronchial plugs (oddly enough, the atelectasis seems to affect the right upper lobe most frequently); (4) if bronchiectasis is thought of, lipiodol bronchography will often provide proof of it; (5) abnormal small intestinal motility.<sup>15</sup>

### Urinary Tract

**Urography as a Test of Function—**Intravenous or excretory urography provides ample opportunity for an evaluation of function of many portions of the urinary tract. It is possible, for instance,

to determine separately the function of the kidney glomerulus and tubules, since it is known that skiodan is filtered out entirely by the glomeruli and that diodrast or neoipax are excreted largely by the tubules. The roentgenographic examination should be planned to show anatomy, disturbance in clearance of contrast media, elasticity, and mobility of structures, and transportation of the dye through the urinary tract. This means films in various positions including prone, Trendelenberg, erect, and oblique.

It is important that some preliminary testing of the patient for sensitivity to the dye be employed. This can be either a conjunctival test with a drop of the dye or an intradermal test read in 20 minutes. In patients with an allergic history or positive preliminary test, it is advisable to give adrenalin subcutaneously before injecting the contrast medium.

Some of the important observations which may be yielded by intravenous urography can be briefly summarized. In patients with recent urinary tract obstruction, an increased infraglomerular pressure will be present, leading to retention of the opaque medium in the kidney parenchyma and the production of a so-called "nephrogram." In cases of delayed clearance of dye from any cause, moreover, it is valuable to obtain films one to two hours after injection of the dye, and see whether more anatomical information may not be forthcoming by prolonging the time of observation. It has been found that the excretion of contrast substances roughly parallels the urea clearance, and that in patients with nitrogen retention, intravenous urography is unsatisfactory. Other factors which may produce delayed clearance of dye through the kidneys are low blood pressure from any cause, parenchymal renal disease, and obstruction in the ureter or bladder. A rough method of estimating the rate

of clearance of the contrast substance is to note the appearance time and density of the dye in the bladder. Information about transportation factors includes estimation of the distensibility and contractility of the renal pelvis, calices, and ureter. It has been shown by kymography that the normal kidney pelvis and ureter contract rhythmically four to eight times per minute, and that alterations in peristalsis are a sensitive index of disease. From the foregoing, it is apparent that there is a wealth of information to be obtained in excretory urography over and above visualization of the anatomy of the urinary tract.<sup>16</sup>

### Pyelography

Retrograde pyelography is an invaluable aid in studying urinary tract disease providing its limitations are known. Inasmuch as this method does not show kidney parenchyma, relatively large lesions can be missed if they do not deform the pelvis or calices. Some other technical and interpretative errors should be avoided. Often the medial border of the dye-filled renal pelvis will show on the film as a straight line which has been mistakenly thought to be caused by hypertrophy of the iliopsoas muscle with a partial obstruction at the ureterokidney pelvic junction. Actually, this straight line disappears when the patient is radiographed in positions other than the supine. The explanation of this phenomenon is to be found in the layering effect which takes place when the contrast substance and urine are mixed. Since the dye is heavier it is found in the dependent portions of the kidney, and the anteromedial portion of the pelvis at the junction of the ureter is not adequately outlined in the supine position. This layering effect can be demonstrated further by taking roentgenograms with the x-ray tube horizontal and the patient

in the decubitus, supine, and prone position.

This layering effect of dye and urine occurs particularly in hydronephrosis, because of the stasis and relatively large amount of urine present. If the patient is not examined in different positions, the full extent of the hydronephrosis will often be missed.<sup>17</sup>

**Cystic Disease of the Upper Urinary Tract**—Under this heading is included pyelitis cystica and ureteritis cystica. Urinary tract buds, cell nests, and cysts are present in a great many patients, although hitherto unsuspected—as many as 15 per cent of individuals with a history of frank urinary tract infection. The cystic change in the mucosa is a residuum of the inflammatory process and is often responsible for chronic pain and hematuria. The cysts arise from invaginated or misplaced epithelial nests with subsequent degeneration (analogous to the epidermoid cysts found in bones of the skull, for instance). By microscopic examination, the cysts are most frequently found in the ureter; next, in the renal pelvis, and least frequently in the bladder. They are often associated with malignant tumors, though no case of a tumor arising in a cyst has been described. The cysts may occasionally be diagnosed on films made after intravenous or retrograde pyelography, where they show as numerous, tiny, filling defects along the margin of the pelvis or ureter. These defects must be differentiated from those caused by non-opaque stones, air bubbles, blood clots, or multiple papillomata.<sup>18</sup>

### Osseous System

**Gargoylism**—This name is given to a condition of infancy and childhood characterized by maldevelopment of the skeleton, mental retardation, corneal opacities, and hepatosplenomegaly, re-



sulting from deposits of lipid-containing cells due to a disturbance in lipid metabolism resembling Niemann-Pick's disease, Gaucher's disease, xanthomatosis, and familial amaurotic idiocy. The child

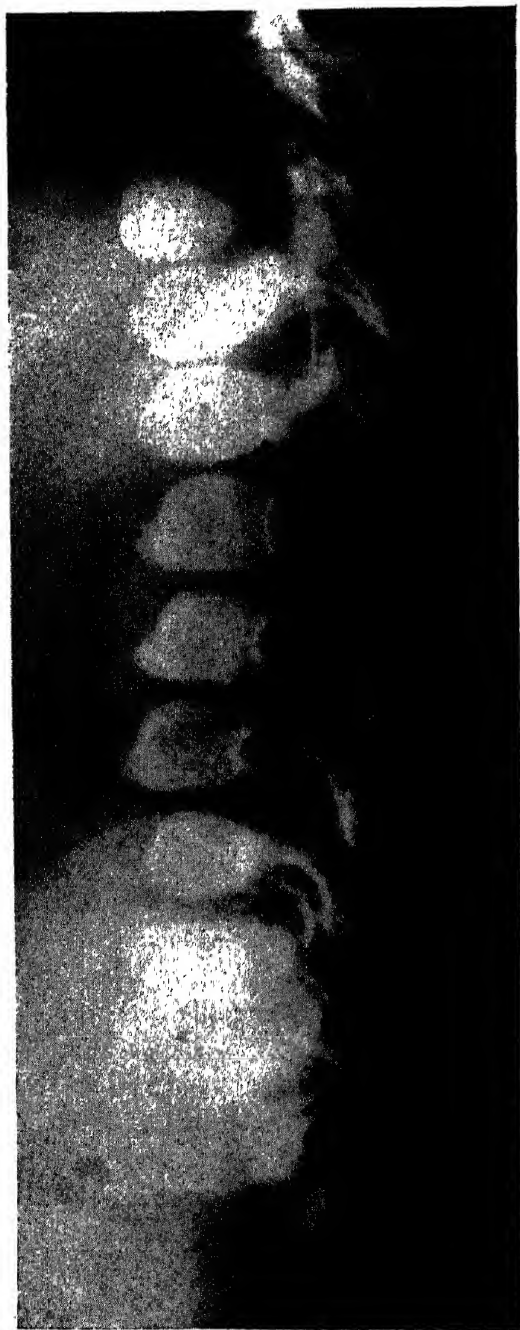


Fig. 4.—Gargoylism. Lateral roentgenogram of spine of 3-year-old boy showing the marked anterior-inferior beaking of the upper lumbar bodies, pathognomonic of this condition. (S. Larson and J. A. Lichty, Jr.: *Am. J. Roentgenol.*)

has the appearance of a disproportionate dwarf with large head, broad face, protruding tongue, delayed dentition, short heavy bones, and dorsolumbar kyphosis. The condition is rare, 38 cases having been reported in the literature, and the roentgen findings are of great help in determining the proper category in which to place patients showing these multiple anomalies. The appearance of the skeleton is that of a congenital chondrodystrophy with a peculiar beaking of the anterior borders of the upper lumbar vertebrae, which is supposed to be pathognomonic.

The differential diagnosis includes cretinism, where dwarfism is more pronounced, and response to thyroid medication prompt, and Morquio's disease, which is also a chondrodystrophy but shows flattened rather than hooklike vertebral bodies.

Treatment of gargoylism has been symptomatic up to the present, but the possibility of causing regression of some of the lipid infiltration (in the cornea, for instance) by roentgen therapy should be considered, because of the success of this method in some of the other lipoidoses.<sup>19, 20</sup>

**Paget's Disease** — It is not commonly recognized that this disease can occur as an entity involving only a single bone. A recent review of nine cases of the monoösteitic variety concluded that in a long follow-up period none of these went on to the polyosteitic form, and that this involvement of one bone was a distinct clinical variant of the textbook picture and might even be more common than involvement of multiple bones. When one bone only is diseased, it is most often in the lumbar spine, and may only be diagnosed by roentgen examination. Two types of bone change are known, the fibrous type which produces softening and eventual compression frac-



ture in the vertebra involved, and which must be distinguished from osteitis fibrosa, angioma, osteomyelitis, and carcinoma, and the sclerotic type to be differentiated from marble bones, osteosclerotic anemias, leukemia, myeloma, and carcinoma. The blood alkaline phosphatase determination which is uniformly high in polyosteitic Paget's is not elevated in the monoösteitic form. The possibility of this disease should be kept in mind when a patient is found to have a pathological compression fracture of the spine following slight trauma.<sup>21</sup>

**Traumatic Lipohemarthrosis**—This condition has been described as occurring after severe injuries to the knee joint. Ordinarily, a hemorrhagic effusion within a joint will show a homogeneous density on the roentgenogram. However, there are several large fat pads about the knee, closely applied to the capsule of the joint, and an injury resulting in tearing of the capsule may at the same time traumatize the fat pads, particularly the infrapatellar, so that liquid fat is squeezed into the joint. When this is mixed with the associated blood, a heterogeneous fluid is formed which tends to separate into layers when the part is immobilized. Advantage may be taken of the diagnostic significance of this layering effect by examining the knee with the patient supine and the roentgen tube horizontal. When the film thus obtained shows fluid levels within the joint, one can be sure that a tear of the synovial lining has occurred, with severe damage to the intraarticular structures.<sup>22</sup>

**Tuberculosis of Greater Trochanter**—Bursitis of the greater trochanter of the femur is rare in contradistinction to the common occurrence of similar disease about the shoulder. When bursitis of the hip is suspected, the possibility of tuberculosis should be considered be-

cause it is much more frequent in this location than at other points where bursae or tendons may become painful. In the examination for disease of the trochanter, films made with soft tissue



Fig. 5.—Monoösteitic Paget's Disease. Lateral roentgenogram of lumbar spine showing a sclerosing cortical lesion with central rarefaction and collapse of the vertebral body. To be differentiated from a malignant lesion. (J. A. Groh: Am. J. Roentgenol.)

exposure are essential in addition to the ordinary roentgenograms, in order that early destruction of the cortex of the trochanter or calcification in soft tissues may be shown. If a careful history elicits the fact that a patient with pain in the hip really has pain *over the hip*, films in internal and external rotation and for soft tissue detail should be made.

The treatment of these cases is often discouraging. Recurrences are frequent after surgical excision for tuberculosis and cutaneous fistulae may develop.<sup>23</sup>

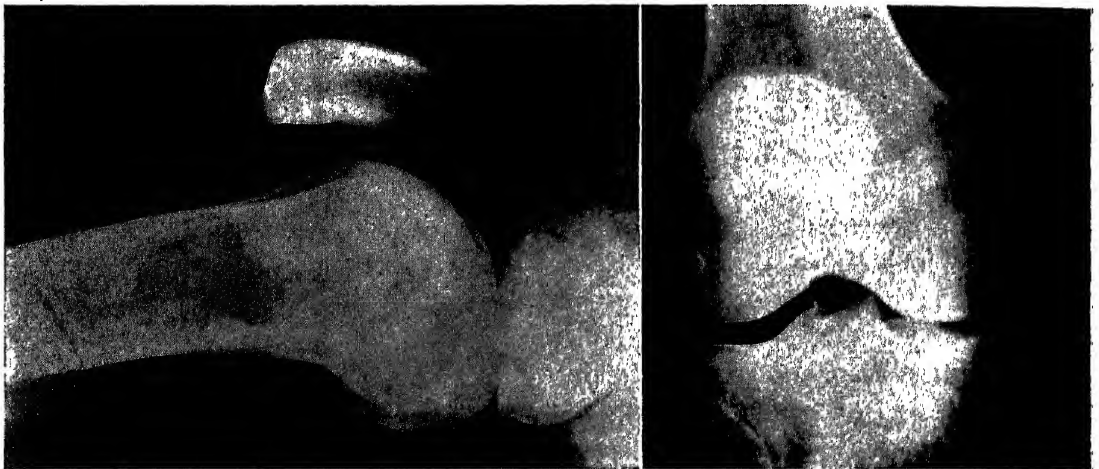
**Yaws**—This is a tropical African disease caused by *Treponema pertenue* and closely related to syphilis in its pathology. The infection is transmitted by flies and affects the cutaneous and osseous system only. Following the fly bite, there is a primary sore and a secondary

rash with eventual development of tertiary gumma-like lesions. The Wassermann becomes positive early, but, like syphilis, the disease may be self-limiting.

In infected soldiers, recrudescences may occur under the stress of wartime activity and the inactive phase of the disease may become lighted up by slight trauma. The commonest bones affected are the tibia, fibula, femur, and ulna.

Another point in distinguishing this disease from syphilis, is the infection of the fibula which is frequent in yaws and rare in lues. Other differential points are the clinical history and response to specific therapy.<sup>24</sup>

**Acrosclerosis**—This is a disease of the subcutaneous tissues characterized by Raynaud's phenomena and scleroderma of the acral parts, face, and neck. Typ-



A

B

Fig. 6.—Traumatic lipohemarthrosis of knee. Fracture through head of tibia. A. Horizontal lateral projection showing gross fluid separation level in supra-, infra-, and retropatellar spaces; marked contusion of subpatellar fat pad with increased radiolucency, probably due to extravasation of fat. B. Anteroposterior roentgenogram showing the transverse fracture of the head of the tibia. (C. B. Pierce and D. C. Eaglesham: Radiology.)

The tertiary infection is marked by the development of a chronic osteomyelitis involving the medulla of the bone primarily, with early dissolution of bone and the appearance of a hole in the shaft surrounded by an eburnated margin. Periosteal proliferation is a late manifestation, in which respect the roentgen appearance differs from syphilis where periosteal reaction is one of the first signs of bone involvement. In long standing yaws, the entire shaft of the bone may have a worm-eaten appearance, or the changes may progress to a bone density similar to marble bones. If the process has softened the bone, deformities due to postural stress will occur.

ical scleroderma is a more diffuse process involving most tissues and organs of the body, with a widespread thickening of the connective tissue. Both conditions occur primarily in young adult females and acrosclerosis has a much better prognosis.

The roentgen changes in acrosclerosis are dependent upon alteration in blood supply to the diseased tissue. There is a diffuse calcinosis with deposits of calcium, particularly in areas of the body where pressure occurs. Irregular decalcification occurs in the long bones with characteristic absorption of the ends of the distal phalanges giving a "pinched off" appearance. Some patients have

shown changes in the lungs which have been considered the result of fibrosis and occasionally stenosis of the esophagus will be found as a part of the clinical picture.<sup>25</sup>

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## ROENTGEN THERAPY

ROBERT P. BARDEN, M.D.

### Physical Apparatus

**Ionization Oscillograms**—Heretofore, studies of the output of roentgen ray tubes have relied on measurement of the ingoing electrical energy. Since it has been shown that the wave form of the energy applied to the tube is not necessarily the same as the wave form

of the energy emerging from it, it became necessary to design a simple apparatus which would allow immediate observation as well as photography of the time-intensity pattern of the roentgen ray emission. This apparatus consists of a thimble ionization chamber plus a new type high gain amplifier plus a cathode ray oscilloscope.\*

This detector has proven extremely useful in checking output patterns of transformers and tubes. With it, for instance, one can determine whether a constant potential roentgen ray unit maintains this capacity at high as well as low energy outputs. Faults in diagnostic equipment may be located quickly by the oscillograph and its widespread use would materially reduce the time required in servicing roentgen equipment.<sup>1</sup>

**The Betatron**—This machine represents the latest development in the study of the acceleration of small particles. It is a physical apparatus for the tremendous acceleration of electrons, which may turn out to have useful therapeutic application. It consists essentially of a powerful magnet between whose poles a stream of electrons is fed. By rapidly alternating the magnetic field, the electrons are accelerated progressively within an ever-widening orbit. The ultimate velocity attained by the electrons may be very close to that of light. This accelerated stream of electrons can be focused or deflected by suitable magnetic force which renders it more easily controlled than other forms of energy, such as roentgen rays or neutrons. A 20-million-volt Betatron, operating at a frequency of 180 cycles per second, can produce, by bombardment of a suitable target by its ejected stream of electrons, an x-ray

\* Note: The reader is referred to the original article for photographs and wiring diagrams of the apparatus.

output of 50 r per minute at 70 cm. from the target. The roentgen rays so produced go forward in a pronounced beam with very little scattering in air. There are plans, now, for building a 100-million-volt Betatron for the study of cosmic ray phenomena.<sup>2</sup>

The ideal in therapy would be to fire the electron beam from the Betatron directly into the patient instead of first transforming the energy into roentgen rays. Such a beam of electrons generated at 20 million volts would penetrate 10 cm. below the skin. Because of technical difficulties in collimating and controlling the electron beam, however, its use in clinical practice is not possible now. It has been shown that scattering from the roentgen beam generated by the betatron occurs in such a way that the dose 4 cm. below the skin is three to four times the skin dose. Depth dose measurements of this x-ray beam with a phantom and a portal 1 sq. cm. show the percentage at 10 cm. as follows:

Generated at 5 million volts = 80% of skin  
 Generated at 10 million volts = 120% of skin  
 Generated at 15 million volts = 170% of skin  
 Generated at 20 million volts = 220% of skin

Such figures give some idea of the tremendous potentialities of this apparatus when compared with the average depth dose of 30 per cent obtained with the usual present-day deep therapy equipment.<sup>3</sup>

### Supplementary Technics

#### Decreased Skin Radiosensitivity—

There are three methods of increasing the dose of radiation to a deep-seated tumor. The first of these is by using rays of shorter wave length and this requires expensive supervoltage apparatus. The second is by increasing the relative sensitivity of the tumor in relation to the skin, and although many methods have been tried to reach this end, none are

reliable enough for routine use. The third, and extremely simple method, is to decrease the sensitivity of the overlying normal tissues, particularly skin and mucous membrane. Some accepted ways of increasing resistance of skin to roentgen rays are by the application of cold, pressure, or production of ischemia by other means. It is suggested that the use of a simple salve containing adrenalin may be a useful supplementary technic for avoiding untoward surface reactions during roentgen therapy. The prescription is as follows:

R Adrenalin ..... 0.01 cgm. (0.0015 gr.)  
 Stovaine ..... 1.00 cgm. (0.15 gr.)  
 Benzoinated  
 lard ..... 100.00 Gm. (15 gr.)

This salve is massaged lightly with cotton over the treatment area before each treatment. The efficacy of its use is shown by the halo of epidermitis which may occur occasionally at the periphery of a treatment field not completely covered by the salve, while the center of the field is not even pigmented. With careful application and repeated use, the salve should allow an increase from the usual 2000 r to a maximum of 4000 r, total dose, on a field of 20 sq. cm. with 200 kv. and 1 cu. filter.<sup>4</sup>

### Applied Anatomy

**Vertebral Vein System—**The consistent pattern of the spread of carcinoma of the prostate to the pelvis and lumbar spine is well known. It struck one observer that this pattern mirrored the distribution of the extensive plexus of veins within the pelvis and along the lumbar spine. Experimental proof was obtained by injection methods. Since the deep dorsal vein of the penis is an integral part of the prostatic venous plexus, material injected here could be traced throughout all the ramifications of the venous plexus and the distribu-

tion of the injected material was seen to mimic the spread of prostatic metastases.

Anatomically, this vertebral venous plexus anastomoses with the vena cava at each vertebral body and blood flows in either direction, depending on the differential pressure within the abdominal cavity. This explains why metastases may reach the skull without going through the lungs, and incidentally is a method of explaining all so-called "paradoxical" metastases without recourse to the assumption of a patent foramen ovale in the heart.

In another experiment, material injected into the subpapillary veins of the breast found its way into the vertebral venous plexus, demonstrating the route of extension of metastases from this organ to the skull and rest of the skeleton. This concept recalls the widely known permeation theory of Handley as an explanation for the spread of breast carcinoma through lymphatics, and the present suggestion is that the fundamental idea of permeation was correct, but that a large part of the spread occurs through the veins rather than the lymphatics.<sup>5</sup>

### Brain Tumors

**Medulloblastoma** — The radiation treatment of cerebellar medulloblastoma is a very important aspect in the treatment of these usually inoperable lesions. This tumor is very vascular and cellular with the formation of characteristic histologic "pseudorosettes." It is quite radiosensitive and amelioration of symptoms for a long time and occasional cures may be expected by properly planned roentgen therapy. Since widespread metastases to the rest of the brain and spinal cord often occur, this factor should be considered in treatment. Metastases to bone also occur and may occasionally

produce a picture indistinguishable from Ewing's tumor or neuroblastoma.

The commonest presenting symptoms of a patient with medulloblastoma are those arising from increased intracranial pressure and ataxia.

Irradiation is given most intelligently after operative decompression and verification of the type of tumor present. The roentgen therapy should include the entire spinal cord because of the high incidence of "seeding" metastases from malignant cells which float downward in the spinal fluid. Roentgen therapy is best begun four to six weeks postoperative with three cerebellar and two cerebral portals each receiving a total of 2000 r, and covering the entire brain. Subsequently radiation is directed over three fields covering the entire spine to a similar total dose. It is wiser to begin each new portal with small doses, say 50 r, and gradually work up the daily dose to as much as 200 r to each of two fields. An attempt should be made to deliver a total tumor dose of 4000 r to the region of the fourth ventricle. The entire course usually takes a month to complete and the patient should be kept in the hospital for the entire time because of the danger of sudden edema of the brain following irradiation. This is particularly liable to occur during the initial few days of treatment. Because of the large area of membranous bone included in the treatment fields, a careful check of the blood should be made to detect any rapid fall in the red or white cells, indicating serious damage to the bone marrow. It is advisable to repeat the entire course in four to six months, even if the patient appears to be in good health.

An analysis of 56 proven cases showed definite prolongation of life from an average of one year in untreated cases to two and one-half years in patients who re-

ceived more than 3000 r to the tumor with additional treatment of the cerebrum and spine.<sup>6</sup>

### Lung Conditions

**Asthma**—The use of radiation therapy in chronic asthma is recommended and this is based on the good results due to the influence of the x-rays on the infection which so frequently accompanies this disease. Preliminary films of the sinuses and chest should be obtained and where chronic hyperplastic sinusitis is present, this should receive roentgen therapy also. Of 100 cases with average duration of asthma of 12 years, 58 had elevated white counts which fell to normal after treatment and as the patient's symptoms improved.

The technic of treatment includes the use of large fields, two anterior obliques at 45°, two posterior obliques at 45°, and two lateral. Each of two fields should be given 100 r daily until a total of 800 to 1600 r has been given to the patient. There is usually a temporary increase in the amount of mucous sputum for two to three weeks following treatment and then a gradual decline of sputum with a loss of all asthmatic symptoms. One to three such courses may be given during a 12-month interval with expected end results as follows: 39 per cent, excellent; 40 per cent, good; 13 per cent, fair; 6 per cent, poor; 2 per cent, no benefit.<sup>7</sup>

### Bone Tumors

**Giant Cell Tumors**—A recent study of this condition based on 29 cases with long follow-ups showed 14 with good results from x-ray therapy alone, although intercurrent fractures occurred in some of these. Fourteen treated by combination surgery and roentgen therapy also showed good results but with a greater number of intercurrent fractures

and infections. Two cases of the series underwent malignant change, one six years and the other nine years after treatment. Regardless of the method of treatment, one of the most important procedures was adequate splinting of the affected bone until healing occurred.

Where roentgen therapy is used alone, the total dose seems of little importance, one of the cases with a good result receiving as little as 600 r. If the total dose does not exceed 2000 r, there is little danger of disturbing the growth of an ununited epiphysis. It should be noted that the immediate result of x-ray therapy, especially if large doses are used, may be an alarming osteoclasia in the tumor-bearing area, but if patience is exercised and surgery deferred, the bone will heal even after a year has passed. In general, children seem to heal more rapidly than adults after any form of treatment. If it is decided to use surgery as the initial treatment, postoperative irradiation is not indicated.

There is no way of determining in advance which of the tumors will undergo malignant degeneration (two out of 29 in this series). Often tumors which may be benign will destroy the overlying cortex and cells from these tumors may be found in veins. Occasionally, this still benign tumor will cross a joint and invade the adjacent bone, but it never extends across an ununited epiphysis.<sup>8</sup>

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## SURGERY

## ABDOMINAL SURGERY

Edited by JAMES NORMAN COOMBS, M.D., F.A.C.S.

## APPENDICITIS

O. P. LARGE, M.D.

**Incidence**—The high incidence of this disease in the United States has made the management of the disorder of greatest importance to the medical profession, especially to the surgeons. Appendicitis in the United States in 1939 stood fifteenth as the cause of death, with 14,113 fatalities.

age was 67.5 per cent. However, in the 228 patients in the younger group the incidence was only 28.8 per cent. (Powers<sup>1</sup>.)

**Etiology**—Most of our knowledge concerning the causative factors of appendicitis has been gained by examination of pathologic specimens removed during various stages of the disease.

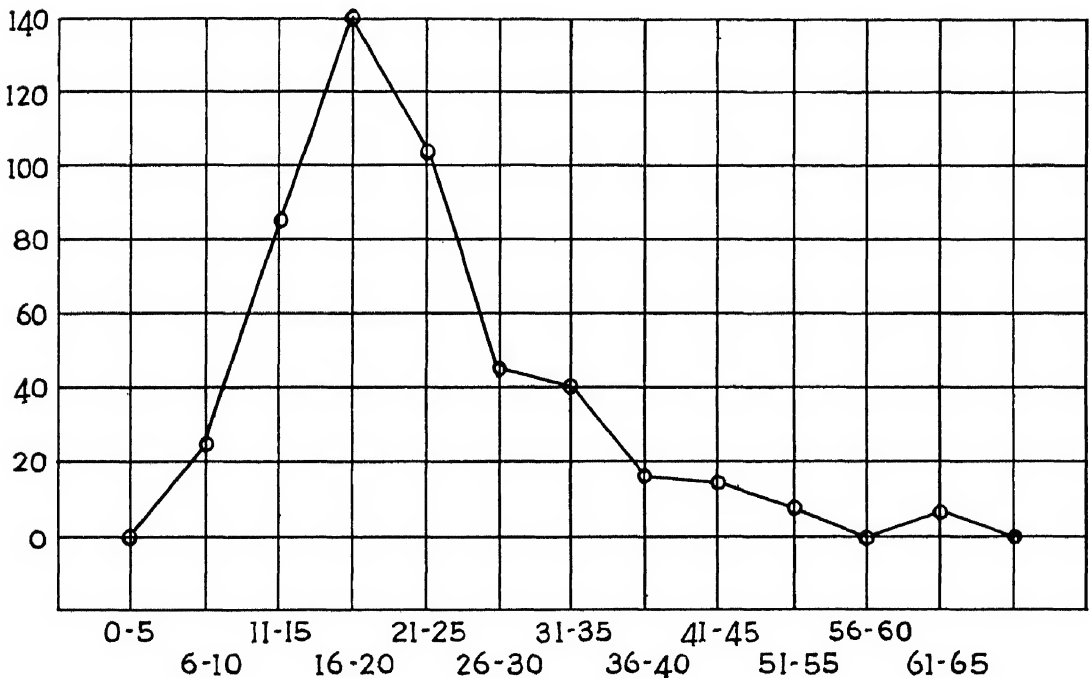


CHART 1

AGE DISTRIBUTION IN 500 CASES OF NONRUPTURED APPENDICITIS  
(Gardner, C. E., Jr., and Sapp, C. J.: Am. J. Surg.)

The age distribution of most of these cases falls between the ages of 15 and 25. However, the disease does occur in children under 15 and in adults over 50, with such frequency that it makes the most common abdominal emergency in both groups.

The incidences of perforation among 40 cases who were 50 or more years of

*Oxyuris vermicularis* does cause typical lesions in the mucosa of the appendix, especially in patients under 15 years of age (chiefly girls). Ashburn reports an incidence of 7.94 per cent in 2317 surgically removed appendices. Another series by Hillman reports 2.39 per cent. The presence of oxyurids in many normal appendices without causing any



typical lesions makes one feel that their presence is only part of the generalized infestation of the large intestine.

Obstruction of the lumen by impacted fecaliths, lymphoid hyperplasia, foreign bodies, strictures, and by serosal adhesions or bands resulting from old inflammatory processes or abnormalities is the most common etiologic factor. The symptomatology of such cases is quite similar to that found in obstruction of any mucous lined canal, namely, colic (cramplike pains), which unless relieved early in course of the disease leads to impairment in circulation distal to the site of obstruction, with resultant necrosis, gangrene, and perforation.

**Bacteriology**—Altemeir,<sup>2</sup> in his study of pathogenicity of the aerobic and anaerobic bacteria, most frequently isolated from peritoneal exudate of perforated appendices, found that the acute peritonitis appeared to be an infection resulting from the synergic activities of *B. coli*, and various other symbiotes present in the appendix.

**Pathology** — Inflammatory changes occur with such frequency in disease of the appendix that they should be familiar to everyone entrusted with the treatment of this common ailment. Lahey<sup>3</sup> classifies appendicitis into three kinds: (1) Hypertrophic parietal appendicitis of Letulle or simple appendicitis of Sonnenburg; (2) suppurative perforating appendicitis of Sonnenburg, and (3) gangrenous appendicitis.

The neoplastic lesions (carcinoma), less commonly encountered, have been classified into three types (Uihlein and McDonald<sup>4</sup>): (1) Carcinomas of carcinoid type; (2) carcinomas of cystic type (pseudomyxomata peritonei); (3) carcinomas resembling those malignant forms found elsewhere in the colon. In a series of 144 specimens removed at operation, between 1910 and 1941, at the

Mayo Clinic, 127 (88.2 per cent) were of the carcinoid type, 12 (8.3 per cent) of cystic type, 5 (3.5 per cent) of the colonic type.

Jalaginer speaks about acute catarrhal, suppurative, ulcerative, and gangrenous appendicitis. Chutio divides appendicitis into catarrhal or exudative, perforating and gangrenous. Becerra<sup>5</sup> finds that acute catarrhal and suppurative ulcerous appendicitis is quite common but true gangrene is seldom found in daily practice. Instead, there is another form he calls necrobiotic, which is encountered in 8 per cent of operations. As a causative factor he gives thrombosis or embolism of appendicular artery, extensive compression of vessels, coproliths, torsion, or adhesions. One cannot speak of gangrene because there are not yet infectious symptoms. The onset of gangrene is necrobiotic appendicitis, caused by spreading of anaerobic infection, which changes the picture clinically to one of utmost gravity.

Polyposis of the vermiform appendix is an extremely rare finding. Collins, in 1932, was able to collect only 17 such proven cases. The recorded cases show that in 14 patients the ages ranged from six to 40 years, and four from 60 to 80 years. There were nine males and ten females. In 14 cases the polyp was located in the proximal third of the appendix; in three cases it was middle third, and in two cases in the distal third. Most polyps measured from 0.5 to 3 cm. in length.

Hopping, Dockerty, and Masson<sup>6</sup> claim that carcinoids of the stomach, small intestine, and colon frequently are classed as being malignant, but exactly similar lesions in the appendix are often regarded as benign. They have recorded instances of no less than 16 metastasizing appendiceal carcinoids bearing witness to the seemingly innocent neoplasm capable

of widespread dissemination. When it does occur it is usually local in mesenteric fat, lymph nodes and more rarely to the liver.

Latimer reports three new cases of malignant argentaffine tumors of the appendix, one a case of a 38-year-old male presenting himself with acute abdominal symptoms suggesting appendicitis without nausea, vomiting, or change in bowel habit. Pathological report showed acute appendicitis superimposed upon a malignant argentaffine tumor of the appendix. The second case was operated during the interval stage and showed a malignant argentaffine tumor of the appendix. The third patient, a white woman 63 years of age, was admitted with acute symptoms referable to the lower right abdominal quadrant, and a fibrotic type of appendix was removed. The pathological diagnosis was malignant argentaffine tumor of the appendix. The argentaffine tumors occur most often in the appendix, but they also occur in the stomach, small bowel, Meckel's diverticulum, colon, and gall-bladder. These tumors are present in 0.2 to 0.5 per cent of all appendices removed surgically. Complete surgical removal is the treatment of choice in all argentaffine tumors.

According to Skarby,<sup>7</sup> 61 cases of true primary or secondary appendiceal intussusception have been reported. Of these, only 20 were definitely primary types. He reports a case which presumably is the first diagnosed by x-rays. The patient was a 68-year-old female with a past history of mild perityphlitis at the age of 20 without any intervening abdominal symptoms. She complained of recurrent severe colicky pain without vomiting. Between attacks she was free of pain. Several gastrointestinal studies were made, which showed narrowing of the proximal lumen of the appendix with a typical filling defect in the cecal wall

which indicated invagination. On one occasion tenderness was present. The four types of appendiceal intussusception are: (1) Invagination of the appendix on itself; (2) protrusion of the appendix partly or entirely in the cecum; (3) invagination of the appendix plus the portion of cecal wall adjacent to the appendix base, and (4) intussusception of the appendix in association with intestinal intussusception. In the first three groups the appendix is the primary intussusception. The treatment of the condition is reduction of the invagination and appendectomy. Sometimes it is necessary to do a limited cecal amputation. Fixing of the cecal wall may be advisable in certain cases.

**Diagnosis**—Appendicitis is a treacherous disease, unpredictable with regard as to when, if ever, it will perforate. Ofttimes its manifestations are so bizarre as to simulate every acute abdominal condition and confuse the most clever clinical observers. The tragic mistakes in diagnosis are usually made in the age groups under 10 and over 50 years of age. In a series of 500 cases (Gardner and Sapp<sup>8</sup>), one case in every 15 was under 10 or over 50 in the unruptured group. In the ruptured group the ratio was one in four cases. The following chart shows the high mortality in age groups where appendicitis is not suspected or considered.

CHART 2

<i>Age</i>	<i>Per cent All Non- ruptured</i>	<i>Per cent Ruptured</i>	<i>Per cent of Those Who Died in Ruptured Groups</i>
1 to 10	5.0	15	30
50+	1.6	10	18
Total	6.6	25	48

Generalized pain (cramplike) often prominent in epigastrium, which localizes in the right lower quadrant, is the most significant and important finding in making a diagnosis (Duley<sup>9</sup>). Any subsidence of pain should make one suspicious of impending perforation and gangrene, instead of subsidence of the attack. Pain in patients over 50 showed less tendency to localize (Powers<sup>11</sup>).

Nausea and vomiting, instead of pain, often cause the patient enough discomfort to seek medical advice. Fifteen per cent of these cases blame this nausea and vomiting on dietary indiscretion (Slattery and Hinton<sup>10</sup>).

Leukocytosis has been stressed by many authors, in both current literature and textbooks. In making a diagnosis of appendicitis, however, here are some of the facts. In 15 per cent of cases in which acute appendicitis was found at operation, 9 per cent had no leukocytosis. In 96.5 per cent of cases of nonperforating gangrenous appendicitis of less than 12 hours' duration, the leukocyte count was above 10,000; of the cases of nonperforating gangrenous appendicitis with a history of more than 48 hours, only 55 per cent had a leukocyte count of over 10,000 (Cedarlund<sup>11</sup>). Leukocytosis, then, was found more constantly in those cases with a history of short duration. Cedarlund concludes therefore that in cases of long duration the leukocyte count is inconclusive.

Tenderness, spasm, and rebound are present in only 30 per cent of cases (Slattery and Hinton<sup>10</sup>). Delaying diagnosis by waiting for these and other classic physical findings will result in a large percentage of peritonitis. These symptoms only are present when peritoneal involvement has begun. These symptoms and signs are usually absent or obscure in retrocecal position of the appendix. According to Gardner and

Sapp,<sup>9</sup> one case in every 17 cases of appendicitis has blood in the urine when the appendix is approximating the ureter.

Deep palpation of the area just internal to and above the crest of the anterior-superior spine provokes an objective pain that is quite localized and diagnostic of appendicitis. This reaction is completely independent of location of the appendix. Lesions of appendix cause hyperesthesia in the posterior abdominal partial peritoneum overlaying the iliacus muscle. Capurro<sup>12</sup> found at operation that injection of 1 per cent novocaine into the mesoappendix causes this hyperesthesia to disappear. The logical deduction was that if there was a zone of sensitivity in this region, blocking the sympathetic pathway should relieve the pain. In his series this fact was proven in 200 cases. This finding is of special significance in cases which show no spasticity of anterior abdominal wall.

**Differential Diagnosis**—Acute mesenteric lymphadenitis and acute appendicitis will tax the acumen of many clinicians. In Tilley's<sup>13</sup> series of cases, 11 of 69 cases of mesenteric lymphadenitis had acute suppurative appendices found at operation. The diagnosis can only be made by careful history and examination. In lymphadenitis the pain is not gripping but aching. There is no definite localization or tenderness. Tenderness may be found along the line of the root of the mesentery, or about the umbilicus. In 36 per cent of cases the onset of pain was in the right lower quadrant, which, in appendicitis, is in epigastrium. Fever is usually higher, above 100.2° F. Notwithstanding the careful examination in such cases a fear of overlooking an acute appendix is responsible for the large percentage of operations in this condition.

**Meckel's Diverticulum**—The true nature of this inflammatory process is usually not discovered until the obvious

necessary exploration is undertaken (Smyth<sup>14</sup>). In mildly congested appendices removed at operation the terminal ileum should be explored for one meter above the ileocecal valve to avoid overlooking an inflamed Meckel's diverticulum. Meckel's diverticulum lies in a bed of small intestines, producing varying degrees of small bowel obstruction and resulting distention out of proportion to other symptoms and signs of appendicitis.

Right-sided ureteral calculus usually is sudden in onset, with severe pain, marked involuntary muscle spasm out of proportion to the tenderness, higher fever, and small amounts of blood or pus in the urine. This, however, cannot be relied upon as a safe differential factor unless confirmed by cystoscopy, retrograde catheterization, and x-ray study.

According to McLaughlin,<sup>15</sup> the ovarian lesions which most often give symptoms suggestive of appendicitis are: Ruptured graafian follicle, corpus luteum cyst, and bleeding corpora lutea. In a study of 49 patients with ovarian lesions

simulating appendicitis the diagnosis of appendicitis was considered in all the cases. It was first choice in 56 per cent, and secondary in 43.4 per cent. Ovarian lesions were considered as the underlying cause in 77 per cent and were the primary diagnosis in 41 per cent of the cases. While he emphasizes that a certain number of these cases may be clinically differentiated from appendicitis and a nonoperative course pursued, it was definitely felt that abdominal exploration was indicated in any case of doubt. If ovarian lesions were found at the time of operation, resection of the cystic portion of the ovary gave freedom of symptoms in 82 per cent of the cases studied. The essential differences between cyst of the ovary and appendicitis are well outlined in Tables I and II.

A vaginal or rectal examination of the pelvis was not done in more than two-thirds of the group studied, a valuable maneuver having thus been omitted.

Differentiation from acute gastroenteritis, according to Quigley and Contratto,<sup>16</sup> is still not an easy problem. In

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TABLE I  
ESSENTIAL DIFFERENCES BETWEEN CYSTS AND ACUTE APPENDICITIS

<i>Acute Appendicitis</i>	<i>Ruptured Cyst</i>
1. Pain general, later localizing.	Pain local, and remains so.
2. Nausea and vomiting.	Nausea less frequently; vomiting unusual.
3. No discharge.	Spotting occasionally.
4. Tenderness, definite McBurney's.	Tenderness slight; lower.
5. Rigidity.	Absence of rigidity.
6. Temperature and pulse elevated.	Temperature and pulse normal.
7. White blood cells and polymorphonuclears increased.	White blood cells and polymorphonuclears about high normal.

(E. F. McLaughlin: Am. J. Surg.)

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TABLE II  
DIFFERENTIAL POINTS IN CYST RUPTURE AND RECURRENT APPENDICITIS

<i>Recurrent Appendicitis</i>	<i>Ruptured Cyst</i>
1. Irregularity of occurrence.	Sometimes regular.
2. Unrelated to menstrual cycle.	Midperiod or latter half of cycle.
3. Right side.	Occasional left-sided attack.
4. No discharge.	Spotting or discharge with attack.
5. Occasional acute attacks.	No typical appendiceal attack.
6. No masses.	"Phantom" tumor.

(E. F. McLaughlin: Am. J. Surg.)

review of 100 cases of acute gastroenteritis and 60 cases of appendicitis, they would anticipate acute gastroenteritis if the onset was explosive with colicky abdominal pain, vomiting, diarrhea, high fever, white cell count below 10,000, and bizarre or absent abdominal signs.

### Treatment

It is generally accepted that *immediate operation* is indicated in all cases of unruptured, acute appendicitis, with or without peritonitis, unless obviously moribund. In ruptured cases, with foul-smelling seropurulent exudate in the peritoneal cavity or other evidences of gross contamination from perforation, there is a difference of opinion as to the advisability of removing the appendix or being content with *drainage* alone. The decision is usually influenced by accessibility of the appendix, and the condition of the patient. Nassau *et al.* found the mortality rate in cases of peritonitis, which were not drained, slightly lower than in drained cases. Babcock has pointed out that drainage is usually unnecessary in the cases of gangrenous appendix, or one in the early stages of perforation, when the peritoneal exudate is purulent and odorless. Conventional rubber tube, or cigarette, drains set up peritoneal reaction which quickly walls off and leaves outlying pockets of exudate which cannot be evacuated. This is especially true of collections in the cul-de-sac. This condition has been greatly improved by the sump alloy steel drain (Babcock).

Treatment of subacute and chronic appendicitis is well illustrated by Willauer and O'Neill<sup>17</sup> in a series of 375 cases with diagnosis of subacute or chronic appendicitis. The hospitalization preoperatively was 12 days or longer, giving the ward surgeon from two to four days for diagnosis. All patients were subjected

to special studies; complete cases of all preoperative symptoms were reported in 348 appendectomies (92.8 per cent). The remaining 27 cases obtained no relief.

**Technic**—The technic of appendectomy has changed very little in recent years. Schrager discusses the various arguments in the management of the appendiceal stump. Three interesting complications are reported: (1) A case of peritonitis from rupture of an old infected stump; (2) an enlarged mucocele in the cecal wall originating in an old appendiceal stump; (3) a granuloma in the cecal wall at the site of an old appendiceal stump. To remedy such complications it must be realized that the appendix does not terminate abruptly at the cecum, but often seems to run intramurally. He recommends removal of a small segment of the cecal wall, the opening being closed with purse string suture. This procedure, however, has not been deemed necessary by other surgeons, who advocate simply double ligation of the base and removal by cautery of the appendix without inversion of the stump.

Voldeng<sup>18</sup> points out the importance of outlining the situation of the appendix before operation and believes that it will assist the surgical technic in these two points: (1) An incision would be chosen to give better exposure and more direct approach to the infected area; (2) less intraabdominal manipulation and exploration would be necessary, thus avoiding all possible general contamination. In order to accomplish this, the author gives the patient with a diagnosis of acute appendicitis *morphine*, *atropine*, and one of the *barbiturates* and allows a sufficient time to elapse for these medications to have their full effect before coming to the operating room. Just before the anesthesia is administered an attempt is made to elicit the point of

maximum tenderness. This must, of necessity, also include a rectal or vaginal examination in order to elicit the tenderness produced by a pelvic type of appendix. The information thus obtained is evaluated according to the clinical picture presented in the individual case. In this manner the author feels that many cases of retrocecal appendicitis, pelvic appendicitis, and appendicitis lying in contact with the kidney, ureter, or sigmoid may be diagnosed in the pre-operative period. While the muscle-splitting incision is preferred, its location may be varied according to the findings in individual cases. For the medium-placed appendix a medial or pararectus incision may be desired. In cases of pelvic appendicitis the right rectus or right paramedian incision may be desired.

Bowen has suggested the use of a modified Furniss clamp as a technical aid in appendectomy. He discusses the various features of ligation and inversion of the appendiceal stump but leaves the treatment of the stump entirely up to the discretion of the individual surgeon. Ligation, inversion, or both, may be accomplished by using the modification described.

### Management of Complications

**Peritonitis**—The benefits of *chemotherapy* in peritonitis are well illustrated by statistics from the Mayo Clinic (Waugh, McCall, Herrell<sup>19</sup>) chart.

In 1940 to 1942 series of cases, practically all patients received *sulfanilamide* or *sulfathiazole*, intraperitoneally, and this was followed by additional subcutaneous or intravenous administration of the drug, maintaining adequate concentration in the blood, for at least one week. No marked difference was noted between use of sulfanilamide and sulfathiazole.

CHART 3

MAYO CLINIC: PERFORATIVE APPENDICITIS  
WITH SPREADING PERITONITIS

	Total	Died	Mortality
1936-1939 no, or inadequate	166 chemo- therapys	28	16.9
1940-1942 adequate chemotherapy	132	5	3.8

As a result of the mortality studies in 3795 cases of appendicitis with a mortality of 0.5 per cent, Guerry and McCutchen<sup>20</sup> have outlined some of their ideas concerning the treatment and results. In the series studied, the acute gangrenous ruptured appendix with diffuse peritonitis subjected to immediate operation showed ten deaths in 94 cases, a mortality of 10.64 per cent, while the acute gangrenous ruptured appendix with diffuse peritonitis and deferred operation showed two deaths in 139 cases, a rate of 1.43 per cent. They regard the deferred treatment as the first step in the operative management of acute appendicitis with peritonitis. The diffuse peritonitis may be present for a few hours after the onset of appendiceal disease and may go on to rapid perforation, in some cases many days after the onset of the appendiceal disease, where the perforation was successfully localized immediately, but the growth of the abscess has allowed it to break through its protective barriers into the general peritoneal cavity, and those cases in which evidence of diffuse peritonitis appears three to four days after the onset of the appendiceal disease. In any case the symptoms of peritonitis (distended and rigid abdomen, rapid pulse, high temperature, prostration, and hippocratic facies) will gradually disappear in the

course of a few days if the patient is properly Ochsnerized. While they believe that the majority of cases will go on to complete resolution, they believe operative treatment should be carried out as soon as the acute symptoms of peritonitis have subsided and a localization of the condition occurs. These facts are emphasized in the operative management of the appendiceal abscess: (1) The location of the incision should be directly over the abscess; (2) the extent of the incision should be adequate to provide room for gentle execution of the following steps; (3) mobilization of the head of the cecum is important; (4) adjacent areas should be protected from soiling; (5) adequate drainage by means of cigarette or split fenestrated soft tubing; (6) placing omentum preliminary to closure is important; (7) loose closure of the wound, especially if it is infected.

Treatment of peritonitis resulting from perforation of the appendix is discussed by Jungbluth.<sup>21</sup> He advocates the *deferred method of treatment*. Patients are not operated upon until they are absolutely afebrile. He feels that the longer the infection is allowed to subside the better the results. The value of early operation lies in prevention of perforation and for that reason, according to the author's view, early operation should be ideal.

A review of 1313 cases of clinical appendicitis treated from January, 1935, to July, 1939, showing an overall mortality of 1.75 per cent, was reported by Dennis *et al.*<sup>22</sup> During this period conservative management of most advanced cases was the rule. The mortality rate in cases with extraappendiceal localization (localized peritonitis or abscess formation) was 3.6 per cent and that in cases with generalized peritonitis was 19.1 per cent. Despite the fact that it requires more hospital days, drugs, blood, and care,

conservative treatment was thought to be the treatment of choice in cases of appendicitis where the disease had spread beyond the appendix itself.

Allen and Johnson<sup>23</sup> report an unusual complication. Purulent discharge from the umbilicus secondary to spontaneous rupture of appendiceal abscess or generalized peritonitis.

Complications resulting from surgical intervention are discussed by Ransom<sup>24</sup>:

**1. Diffuse Peritonitis**—This usually results from sudden perforation of the obstructive type of appendicitis and accounts for 95 per cent of the deaths from this disease. The diagnosis of appendicitis with generalized peritonitis is not uncommon. The patient complains of severe generalized abdominal pain, with nausea and vomiting. The abdomen becomes distended, tense, and rigid. There has been a pain which became more marked in the lower right quadrant. Auscultation reveals a silent abdomen. Postoperative complications of generalized peritonitis must be regarded as one of the most serious because the mortality is always high. Fortunately, general peritonitis is not one of the common postoperative complications; when it does occur it may be due to: (a) Contamination of the peritoneum, peritoneal drainage of abscesses; (b) to poor surgery in draining when drainage is not indicated at the time of the original operation, or (c) to an ill-timed operation whereby early adhesions formed an abscess, and what may be a localized infection is converted into a spreading peritonitis. Occasionally, if there is an exceptionally virulent type of infection, general peritonitis will spread regardless of the type of the original operative procedure. The subject of drainage is a controversial matter. At present drainage is less frequent, especially in cases in which diffuse perforation is found at



operation. However, when in doubt do not drain.

Studying peritonitis produced by or following operations may present a variable clinical picture. In the young and otherwise healthy adult patients the usual picture of general peritonitis described above may be observed. However, in elderly persons or those weakened by the infection, fluid and salt imbalance, or by prolonged operation involving excessive trauma and hemorrhage, spreading or general peritonitis may exhibit an atypical course. Here the usual signs of peritonitis are apt to be far less striking than usual. There is commonly some abdominal discomfort and distention associated with absence of peristaltic sounds. Nausea and vomiting are common. The temperature may be high or again it may be slightly elevated. The pulse is rapid, and later becomes thready and uncountable.

**Oschner treatment**, consisting of Fowler position, hot applications to the abdomen, nothing by mouth, liberal quantities of *morphine*, duodenal siphonage, *intravenous glucose* and *sodium chloride solution*, *blood transfusions*, *oxygen*, and drugs of the *sulfonamide* group are indicated.

## 2. Secondary or Residual Abscesses

—These are found to occur in certain fossae or regions of the peritoneal cavity. These abscesses may represent a favorable termination in cases which have been treated conservatively and in which the patient has succeeded in overcoming his infection. They may occur as a postoperative complication following drainage in cases of localized appendiceal abscess and again, regardless of whether the appendix has been removed or not. The common sites of these secondary abscesses are: (a) The pelvis, in which case the abscess occupies the cul-de-sac of Douglas; (b) the left lower quadrant; (c) the subdiaphragmatic spaces, and

(d) the ileocecal regions. True residual abscesses following general peritonitis are often found either in the pelvis or in the subdiaphragmatic spaces. The presence of secondary intraabdominal abscess is suggested by persistent fever in the postoperative period; along with this the patient experienced abdominal pain in the location of the abscess. If the process continues over a considerable time the temperature tends to exhibit septic signs and the patient appears worn and haggard from the effects of continued sepsis.

Pelvic abscesses are the commonest of the residual abscesses which may to a certain extent be accounted for by the Fowler position used in the treatment postoperatively. When suppuration has taken place surgical drainage is indicated. The majority of these inflammatory masses, however, will undergo spontaneous resolution under proper conservative treatment. The diagnosis should be suspected in any patient following operation who continues to run a septic course. Wound infection and other causes of the fever, as urinary tract infection, pneumonia, thrombosis, etc., should be ruled out. Daily rectal examination should be made. The inflammatory mass or infiltration is easily felt as a hard, firm, tender mass bulging in the upper rectum anteriorly. It is usually felt at the tip of the examining finger. Bladder symptoms, such as dysuria, urgency, frequency, may be present. In the latter stages diarrhea is not uncommon. As suppuration occurs the anal sphincter relaxes, the anus becomes patulous. The rectal mucosa becomes edematous, succulent, and has a soft, thick, velvety feel. When these findings are encountered **surgical drainage** is indicated. The author advises abdominal drainage by the extraperitoneal route; however, most men feel that rectal punc-

ture is the most satisfactory procedure.

*Left lower quadrant abscesses* are relatively uncommon. They are usually found in children; frequently they are associated with an abscess which fills the pelvis, then extends upward to the left. If suppuration occurs, *drainage* is necessary through a small muscle-splitting type of incision, being careful to avoid the peritoneal cavity. As a rule, there is no great urgency for surgical intervention. Before proceeding with surgery one should be certain that suppuration has taken place and ample time was allowed for firm adhesions to be formed as protective barriers.

*Subdiaphragmatic abscess* occurs as a complication in about 0.9 of 1 per cent. Many of these do not progress to the stage of abscess. The diagnosis of them may not be recognized. The majority of these abscesses spontaneously subside under *conservative treatment*; however, 25 per cent of them require *surgical intervention*. It is suggested that surgery is justifiable if a subphrenic collection fails to subside within one week. Surgical drainage is accomplished by *extrapleural drainage*. Undrained subphrenic abscesses may rupture in the diaphragm, resulting in empyema, bronchiopleural fistula, pneumonia, and lung abscess.

*Right-sided or ileocecal abscesses* are relatively uncommon as postoperative complications, especially in cases where drainage has been employed. They are most likely to occur when drainage has been omitted at the original operation. In the early stages a definite mass may develop and it may be confused with a wound infection. Symptoms and signs may be similar. Later in the case of ileocecal abscess the abdominal mass becomes recognizable. In either case, whether localized intraperitoneal infection or wound sepsis, the *treatment* is

*conservative*. If an intraabdominal abscess is suspected the usual conservative measures for peritonitis should be employed until definite localization has occurred; later, when suppuration occurs surgical drainage is indicated; the operation should not be performed until one is certain that surrounding adhesions are sufficiently strong.

3. **Disorders of the Liver**—Pylephlebitis and liver abscess fortunately are rarely a complication of appendicitis, but they constitute a serious problem when present. The spread is usually by way of the portal vein following a pylephlebitis. The usual clinical picture of pylephlebitis and liver abscesses is characterized by high fever and chills, usually of an abrupt onset; localized pain and tenderness in the region of the liver, and enlargement of the liver. Jaundice is present in about 36.4 per cent of the cases; when present, it is of a grave prognostic value.

4. **Ileus**—As a postoperative complication this may be of two types: (a) Acute mechanical intestinal obstruction, and (b) adynamic or paralytic ileus. Both may cause death. The diagnosis of ileus in the immediate postoperative period is somewhat difficult, due to the insidious and mild symptoms. Often these symptoms are overshadowed by signs of the original peritonitis; thus the abdominal pain and obstipation are difficult to evaluate. However, during the postoperative period, any increase in pain, especially if of a colicky nature, should be the cause for concern. Nausea and vomiting, if persistent and severe, should suggest mechanical or paralytic ileus. The presence of fecal vomiting is indicative of low obstruction. Abdominal distention is due either to mechanical or adynamic ileus. In mechanical obstruction, auscultation reveals active peristalsis. This examination likewise is of value

in those patients who are not convalescing from an abdominal operation and peritonitis. X-ray examination is of great importance, the simple flat plate of the abdomen taken with the patient in a supine position being usually sufficient. Administration of barium by mouth is absolutely contraindicated. Those obstructions occurring in the immediate postoperative period are usually best treated by the *method of Wangensteen* or preferably by using the long *Miller-Abbott tube*. Simple enterostomy may also effect a cure. In the paralytic form of ileus there is no single point of occlusion in the lumen of the bowel; however, all the walls are dilated and peristaltic activity ceases, due to the loss of contractile power; the intestines dilate and remain motionless. Treatment consists of *Fowler position, duodenal suction, gastrojejunal suction, oxygen*. Drugs, such as *eserine or pituitary derivatives*, are contraindicated because of the danger of spreading infection, if mild peristalsis is stimulated. Moreover, they are inefficient in restoring the normal tone and rhythmic contractions of the bowel. *Morphine*, on the other hand, has a stimulating effect upon intestinal musculature by increasing tone and rhythmic contractions. It also minimizes the discomfort of the indwelling tube and intravenous needles, and should be used freely. Blood protein and chlorides should be maintained at normal levels. *Oxygen therapy* has been recommended.

**5. Fecal or Intestinal Fistula**—This condition is an uncommon complication of operation for acute appendicitis either with or without peritonitis. The incidence is about 0.8 per cent. The commonest cause of intestinal fistula is an infection which produces gangrene and perforation of the bowels. Fecal fistulas usually result from direct extension of

the infection from the appendix to the cecal wall. Fistulas involving the small intestines are more often the result of secondary operation for pelvic abscess or intestinal obstruction and are due to injury of the small bowel at the time of operation. Some authors maintain that a higher incidence of fecal fistulas occurs following the inversion method and less occur as a result of simple ligation. The diagnosis of the fecal fistula is not difficult. Fistulas associated with appendicitis usually heal spontaneously, this being particularly true of the cecal fistula. When healing fails to occur in these cases, there is usually an outgrowth of cecal mucous membrane so that it becomes continuous, with the skin producing the direct or lip type of fistula. In such cases surgical closure may be necessary. Ileal fistulas are likely to be complete and less liable to heal spontaneously. Here the added complications of spur formation, herniation, or obstruction distal to the fistula are mechanical factors which serve to maintain the fistulous opening. They must be recognized and corrected by proper surgical procedures. The fistulas associated with appendicitis should be given a prolonged trial on conservative treatment before resorting to operative closure, even though a surgical repair may be necessary at a later date. A successful result is much more likely to be obtained when the local inflammatory reaction has been given a chance to subside before the operation is attempted.

The subject of intestinal fistula is reviewed by Simon,<sup>25</sup> who reports an unusual case of persistent postappendiceal high intestinal type of fistula and its management. Diseases of and operations on the vermiform appendix still constitute the commonest cause of intestinal fistulas. Intestinal fistulas are growing less common following appendicitis since

the advent of earlier diagnosis and a more simplified technic. Many intestinal fistulas were caused spontaneously, and *conservative management* should be given a fair trial before surgical intervention. The mortality following *surgical closures* ranges from 8.9 to 50 per cent.

**Intestinal Obstruction** — McNealy and Lichtenstein<sup>26</sup> point out that intestinal obstruction following appendectomy is possible as a result of angulation and fixation of the terminal ileum. It may occur soon after appendectomy or a considerable time following the operation. The ileomesenteric and ileoappendiceal folds appear to a greater or lesser extent when the cecum lies medial or inferior to the cecum. Wakely found that 65 per cent of 10,000 cases presented a retrocecal appendix. These cases are not particularly susceptible to this type of obstruction since they do not alter the position of the terminal ileum to any extent. In the remaining one-third of the cases, however, the possibility exists. As a means of preventing this complication, the authors advise individual ligation of the vessels in the mesoappendix rather than mass ligation. They do not feel that it is necessary to attach the mesoappendix to the cecum if careful individual ligation of the vessels is followed. They believe it is better to leave the mesoappendix in an undisturbed neutral position.

**Peptic Ulcer**—A case of perforated peptic ulcer, complicated by acute appendicitis, is reported by Sanders.<sup>27</sup> Nine other such cases found in the literature were analyzed. As a result of this analysis, he points out that the history of previous digestive disturbances is frequently absent. The pain of which the patient complains is often located in two areas, the right upper quadrant and the right lower quadrant. Liver dullness does not always disappear in perforating

peptic ulcer. Preoperative diagnosis in all the cases reviewed was acute appendicitis with or without perforation, and only postoperatively was the coexistence of two lesions found. The right rectus incision was advised, as it allows easier exploration of the abdominal contents. When the pathological condition in the appendix is not sufficient to account for the extent of peritonitis present, it is imperative to search for another lesion in the abdomen, especially the gastroduodenal region. It is wise to operate for appendicitis, acute or chronic, as soon as the diagnosis is made. Mortality and results are best when the operation consists of *appendectomy and simple closure of the perforation*. A number of patients that were followed were found to be symptom-free and some showed normal anatomical and physiological function.

### Mortality

TABLE III  
CHIEF CAUSES OF DEATH

Causes of Death	Number of Deaths	
	From 1931-1939 (In 479 Consecutive Patients)	From 1939-1941 (In 105 Consecutive Patients)
Direct or complication of appendicitis:		
General peritonitis..	13	2
Pylephlebitis.....	4	0
Septicemia.....	1	0
Mechanical ileus....	7	0
Subphrenic abscess..	5	0
Rectovesical fistula.	1	0
Spontaneous rupture of untreated pelvic abscess.....	1	1
Extraappendiceal complications:		
Cerebral accident...	1	0
Pulmonary embolism	3	1
Pneumonia.....	4	0
"Poor-risk" patients	4	1
Cause of death un- certain.....	4	0
Total.....	48	5

(E. S. Stafford: Surg., Gynec., and Obst.)

Jennings, Burger, and Jacobi<sup>28</sup> report 1680 consecutive cases of acute appendicitis with mortality 1.9 per cent. Delay in operation and catharsis are important contributing factors.

Duley<sup>9</sup> gives his mortality:

	Number of Cases	Number of Deaths	Per cent
Without perforation.	300	0	0
Spreading peritonitis	70	10	14.2
With abscess. . . . .	47	4	8.5
Total. . . . .	417	14	3.3

Cutler and Hoerr<sup>29</sup> state that the mortality rate for acute appendicitis, at least at the Peter Bent Brigham Hospital, remains the same as it was 25 years ago despite the advancement in technical surgery. The only way to decrease the mortality rate is to prevent the avoidable deaths of patients who reached the doctor too sick or who take medicine without consulting a physician. Public education along the lines of symptoms and signs of appendicitis is advocated as a method of reducing mortality. Today the proportion of cases with perforation or abscess is still greater than 20 per cent, indicating the need for public education. The study of 14 patients who died during the last three years disclosed that six died of extraabdominal complications, four of peritonitis despite treatment with **sulfonamide** drugs. All but three of the 14 had symptoms for 48 hours or longer before coming to the hospital, and eight had taken a cathartic, several upon the advice of their physician.

Black points out that the mortality rate for appendectomy varies widely from 12 to less than 1 per cent; the lowest rates usually in reports of individual operators, the highest in reports of groups. A part of the explanation is due to the

following: (1) Delays in arriving at a diagnosis and sending the patient to a hospital; (2) poor judgment in evaluating the resistance of the patient; (3) inadequate preoperative preparation of the patient; (4) poor technic; (5) inadequate postoperative support; (6) improper administration of the anesthesia; (7) multiple operations. In the 3148 cases studied, 689 other operations were performed at the same time. It was suggested that a surgical organization should appoint a special committee to study the whole question of appendicitis. The first step should be standard classification of the disease in order that reports may be accurately compared. The committee should outline methods which would obviate the present inconstant results by formulating standardized procedures drawn from methods, suggestions, and experiences of various hospitals and surgeons.

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## BILIARY DUCTS

FREDERICK A. FISKE, B.S., M.D., F.A.C.S.

### Anomalies

Congenital atresia and stenosis of the bile ducts may present two operable types: (1) Those that have a hepatic duct but no cystic or common duct; (2) those that have normal gallbladders, cystic and hepatic ducts, but a common duct that ends blind. A case of the second type is presented by Strauss *et al.*<sup>1</sup> An infant was one month premature, exhibiting jaundice and hemorrhage from birth. Operation, one month after birth, consisted of a **choledochoduodenostomy** around a rubber catheter. The catheter was passed by stool one week postoperatively. At this time jaundice gradually subsided. Postoperative convalescence was complicated by a bronchial pneumonia and coryza. At the end of one year the child was well; the weight was 23 pounds.

The differential diagnosis in these cases consists of: (1) *Icterus neonatorum*, the jaundice usually disappears

by the end of the second week. The liver is not enlarged and the stools contain bile pigments. (2) *Erythroblastosis foetalis* is usually fatal in the first two days or weeks of life. It is marked by jaundice, a large liver, a large spleen, and increased erythroblasts. It may be suspected from the golden colored vernix caseosa and hypertrophied placenta. (3) *Jaundice of the hemolytic sepsis* is differentiated by fever, leukocytosis, progressive anemia, toxicity, and no acholic stools. (4) *Congenital syphilis* may be identified by blood test and roentgenologic appearance of the bones. (5) *Obstructive jaundice* from inspissated bile or mucus may give a picture indistinguishable from atresia, and may require surgery for relief. There may or may not be normal stools in the beginning. This depends upon the duct which becomes occluded.

Jaundice due to atresia may not be present at birth. Operation should be

urged in cases of atresia, despite the fact that only 17 to 20 per cent will be found operable. The reported case is the seventh recorded successful operation for atresia of the bile duct.

An unusual anomaly of the bile ducts found at operation in a 51-year-old female was presented by Niemeier.<sup>2</sup> Indigestion, intermittent attacks of jaundice,

remained in place for several months; following this, patient had no trouble. During operation it was necessary to exclude the condition illustrated in Fig. 4 where, with a very short cystic duct, the neck of the gallbladder is definitely adherent to the common duct. With the gallbladder opened, the orifices of the ducts visualized and demonstrated by the



Fig. 1

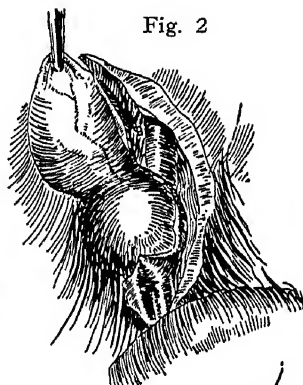


Fig. 2

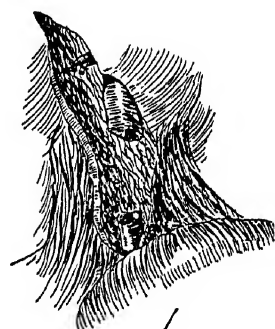


Fig. 3

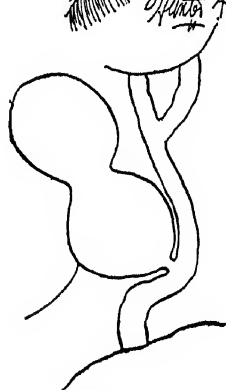


Fig. 4



Fig. 5

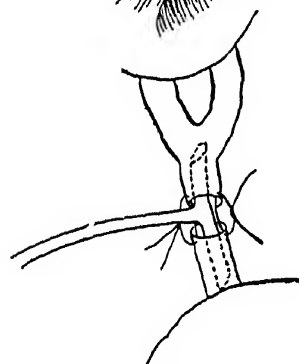


Fig. 6

Fig. 1—Shows duct leaving lower segment of gallbladder and passing down behind duodenum.

Fig. 2—Shows second duct entering lower pouch of gallbladder from above.

Fig. 3—Shows ends of divided ducts as seen after removing gallbladder.

Fig. 4—Condition which had to be excluded, *i. e.*, a short or absent cystic duct with the common duct closely adherent to the gallbladder.

Fig. 5—Shows the arrangement actually present in this case.

Fig. 6—Shows the duct ends being anastomosed over a T tube.

(O. W. Niemeier : Surgery.)

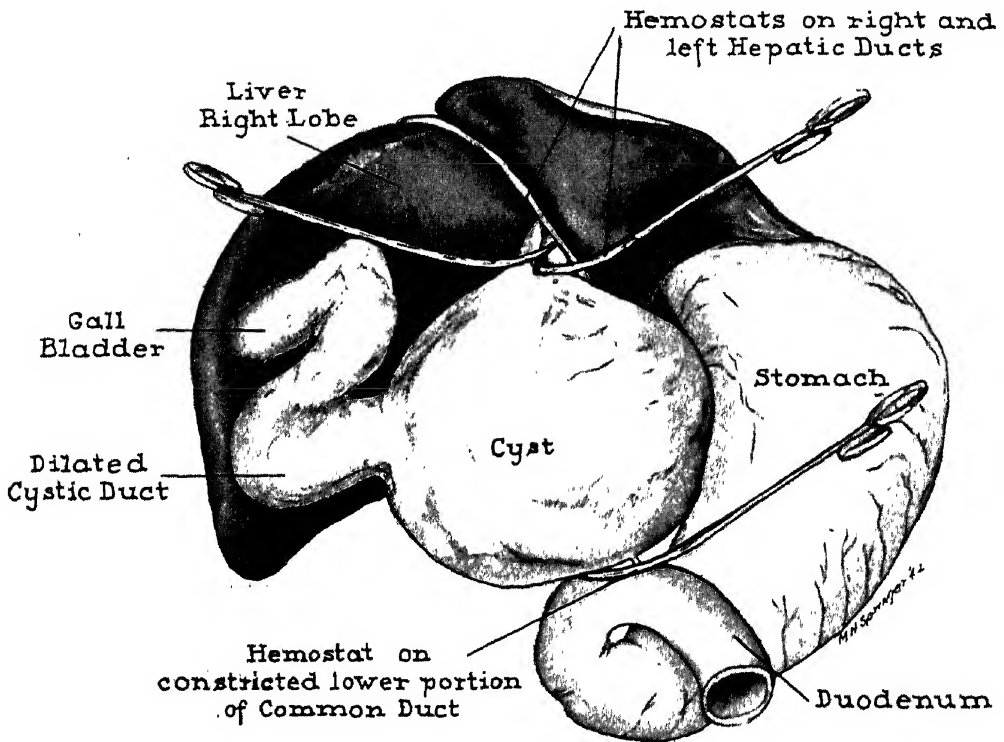
lasting from two to 31 weeks, and jaundice, at the time of admission, with a loss of 20 pounds in weight prior to entering the hospital, were the outstanding symptoms. Pain was not present. The condition found at operation may be visualized in Figs. 1, 2, 3, 4, 5, and 6. Recovery followed complete **cholecystectomy** with subsequent anastomosis of the ducts over a T-tube. T-tube re-

passage of a probe into them, the true situation was clearly apparent. The etiology is of interest since the condition may have been acquired or congenital. The acquired type may have occurred due to a stone in a short cystic duct which progressively enlarged, causing a gradual dilatation of the cystic duct as well as the adjacent common duct and neck of the gallbladder. This may also



be explained as a congenital anomaly. The author felt that the simplest and most logical explanation of the anomaly encountered in this case was probably the congenital absence of a cystic duct. The hepatic duct entered the gallbladder from above and the common duct took exit from its lower aspect, the gallbladder

attack of abdominal pain was eight months prior to admission to the hospital. The pain at this time was followed by the occurrence of a mass and jaundice with slight fever. Jaundice and fever gradually disappeared, but weakness persisted. Mass in the upper abdomen also persisted without pain. Two weeks be-



### Extirpation of Cyst and Gall Bladder

Fig. 7—Extirpation of choledochus cyst and gallbladder, showing clamps on bile ducts before division. (T. A. Shallow, S. A. Eger, and F. B. Wagner: *Ann. Surg.*)

forming the only connection between these two ducts. The stones found in the gallbladder area would explain the occurrence of jaundice in this particular case.

Shallow, *et al.*,<sup>3</sup> reviews 175 cases of *congenital cystic dilatation of the common bile duct*. A case report was presented. The patient was a 20-year-old male, with the chief complaint of pain in the upper right abdomen, a mass in the same area, jaundice, and fever. The first

fore admission to the hospital, the pain recurred, lasting for about eight hours and was severe enough to force him to bed. This was followed as in the previous attack by fever and jaundice. Physical examination revealed slightly undernourished male, temperature 99.4° F., pulse 76, respirations 20. Weight 143. Clinical evidence of jaundice. A large globular mass about 5.6 inches in diameter was visible in the right upper quadrant of the abdomen. It moved on

respiration toward the midline and very slightly downward. It was firm, smooth on palpation, and no definite edge could be made out. Cholecystogram showed nonvisualization of the gallbladder. A mass on the right side of the abdomen was noted. Gastrointestinal series suggested a retroperitoneal sarcoma or pancreatic cyst. Barium enema showed evidence of extrinsic pressure on the hepatic flexure, possibly on the transverse colon. Intravenous urogram showed

moved through a gastroscope. The patient was well 18 months following this first operation. There has been no return of jaundice; he was able to work in a factory.

From the study made, the authors present these summaries and conclusions: (1) The disease predominates in females and occurs principally in children and younger adults. (2) A congenital maldevelopment probably forms the basis of the abnormality. The most plausible ex-

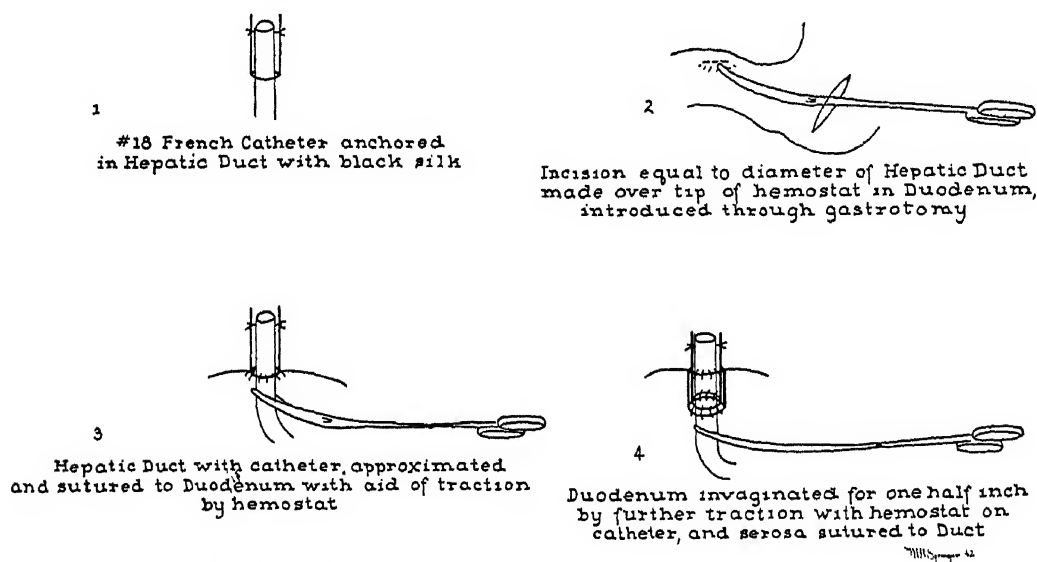


Fig. 8—Steps employed in hepaticoduodenostomy. (T. A. Shallow, S. A. Eger, and F. B. Wagner: Ann. Surg.)

normal kidney function on both sides with possible beginning obstruction of the right ureter. Peritoneoscopic examination showed a retroperitoneal mass in the right kidney of cystic nature, possibly a cyst or a polycystic right kidney. The operative procedure consisted of excision of the cystic mass, gallbladder, and cystic duct; implantation of the right and left hepatic ducts into the first portion of the duodenum over No. 18 French catheters. Fig. 7 shows the condition presenting at operation. Fig. 8 shows the steps employed in the *hepaticoduodenostomy*. Eleven weeks following the first operation, the tubes used for the hepaticoduodenostomy were re-

planation is that of Yotuyanagi, who believes that the etiology lies in the inequality of proliferation of the epithelial cells at the stage of fetal physiologic epithelial occlusion of the common bile duct. (3) The characteristic pathological finding is a large cystic dilatation of the common bile duct. The ducts at the upper pole of the cyst are usually dilated, whereas at the lower pole the intraductal portion of the duct is usually constricted or angulated. Frequently the liver is enlarged or may show biliary cirrhosis. (4) The salient symptoms and signs form a diagnostic triad—tumor, jaundice, and pain. Acholic stools may occur, and bile may be present in the

TABLE I  
DIAGNOSES MADE IN 175 CASES

Preoperative Diagnosis	No. of Cases	Percentage
1 No diagnosis or none stated	59	34
2 Miscellaneous incorrect diagnoses	35	20
3 Choledochus Cyst { First diagnostic impression Mentioned as possible or suspected.	15 7	8.6 4.0
4 Echinococcus Cyst	17	9.7
5 Cholecystitis or Cholelithiasis	15	8.6
6 Pancreatic Cyst or Tumor	12	6.9
7 Stone in Common Duct	6	3.4
8 Retroperitoneal Cyst Tumor, or Sarcoma	6	3.4
9 Hydrops or enlarged Gall Bladder	4	2.3
10 Cyst of the Liver	3	1.7
11 Obstructive Jaundice	3	1.7

(T. A. Shallow, S. A. Eger, and F. B. Wagner: Ann. Surg.)

urine. The symptoms may begin early in life and occur intermittently over a period of years. Roentgenologic studies and peritoneoscopy may be of aid in confirming the diagnosis. The diagnosis was made or suspected in only 22 cases (12.6 per cent), but consideration of the condition as diagnostic possibility should lead to more frequent correct diagnosis. The differential diagnoses made are well illustrated in Table I. (5) The procedure of choice in treatment is a primary anastomosis of the biliary and intestinal tracts. Anastomosis of the cyst itself to the duodenum is accompanied by the lowest mortality, but in good risk patients, extirpation of the cyst with primary anastomosis to the duodenum is preferable because the cyst may harbor infection and regurgitated food. The latter procedure was performed with recovery in the case presented. (6) The mortality in the entire series was 58 per cent, but in those patients treated by primary anastomosis of the biliary and intestinal tracts, the mortality was 27 per cent. The prognosis depends upon the preoperative recognition of the lesion, the condition of the patient at the time of operation, and the type of therapy instituted.

An unusual cyst of the ampulla of Vater is presented by Brooks and Weinstein.<sup>4</sup> The patient, aged 30, complained of repeated attacks of abdominal pain, accompanied by nausea, vomiting, and possibly jaundice. The symptoms were recurrent for a period of one year. However, the patient had a severe attack of pain at the age of 15 for which a cholecystostomy was performed. This is suggestive of a polypoid tumor which was overlooked. Ten months before admission to the hospital, a diagnosis of peptic ulcer had been made. The patient was placed on a Muelengracht diet without relief of his pain. There had been a loss of 40 pounds in weight. Examination of the abdomen failed to reveal any abnormality. A cholecystogram showed a faint shadow of the gallbladder. Gastrointestinal x-rays showed dilatation of the duodenum and proximal portion of the jejunum with a curious filling defect in the duodenum which was not seen until after operation. At operation the duodenum became greatly enlarged about one inch beyond the pylorus, the diameter of the duodenum being almost that of the stomach. The duodenum was mobilized by dividing the posterior peritoneum. It was delivered into the wound.

A longitudinal incision about 10 cm. in length was made through the anterior duodenal wall. A large polypoid mass attached to the posterior wall of the descending portion of the duodenum was found. The entire polypoid mass was covered with what appeared to be normal duodenal mucosa. At the apex of the

was noted that there were two small openings in the central cavity. These openings were approximately 2 mm. apart, one being slightly larger than the other. A probe passed into the larger opening followed the pedicle of the tumor into what appeared to be a normal common bile duct. A probe passed into the

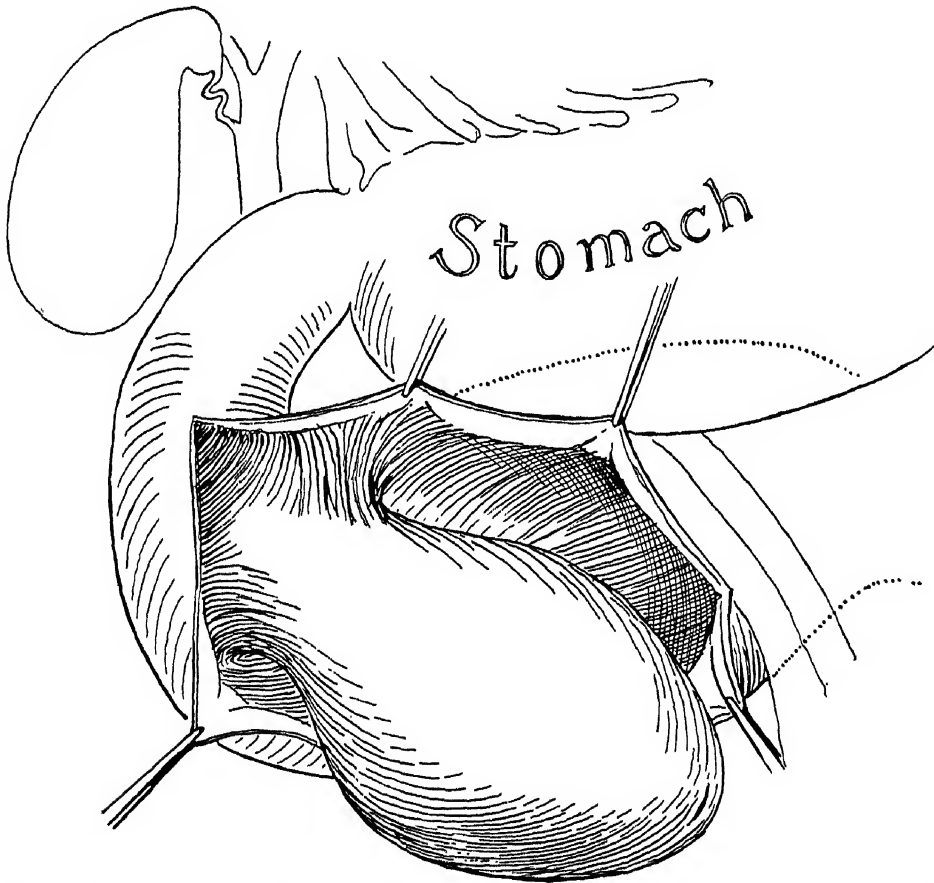


Fig. 9—Diagrammatic illustration of the appearance of the duodenum, after it was opened. The polyp was relatively longer and had a more bulbous tip than is shown in the illustration. The slitlike opening is almost as obscure in the illustration as it was in reality. (B. Brooks and A. Weinstein: *Ann. Surg.*)

tumor there was a slit-like opening which, after its edges were separated, permitted the discharge of a large amount of golden-yellow bile. An incision was made through the anterior aspect of the tumor and it was found that the central portion of the tumor was occupied by a cavity lined with mucosa, which had the same appearance as the mucosa of the duodenum. On careful examination it

other opening apparently followed the direction of the duct of Wirsung. The cavity within the polyp communicated with the lumen of the duodenum by means of a slit-like opening at the tip of the tumor. A circular incision was made about the apertures of the common duct and pancreatic duct, and all the mucosa lining the central cavity, except that contained within the circular inci-

sion, was removed. The greater portion of the mucosa covering the polypoid mass was then removed. This resulted in what appeared to be a linear incision of the mucosa of the posterior wall of the duodenum, within which there was a separate island of mucosa derived from the mucosal lining of the central cyst. The

closed in layers. The patient was discharged on the twelfth postoperative day. During the year following the operation the patient enjoyed excellent health and gained 40 pounds.

While the authors presented this as a cyst of the ampulla of Vater, they felt that most of the findings and the symp-

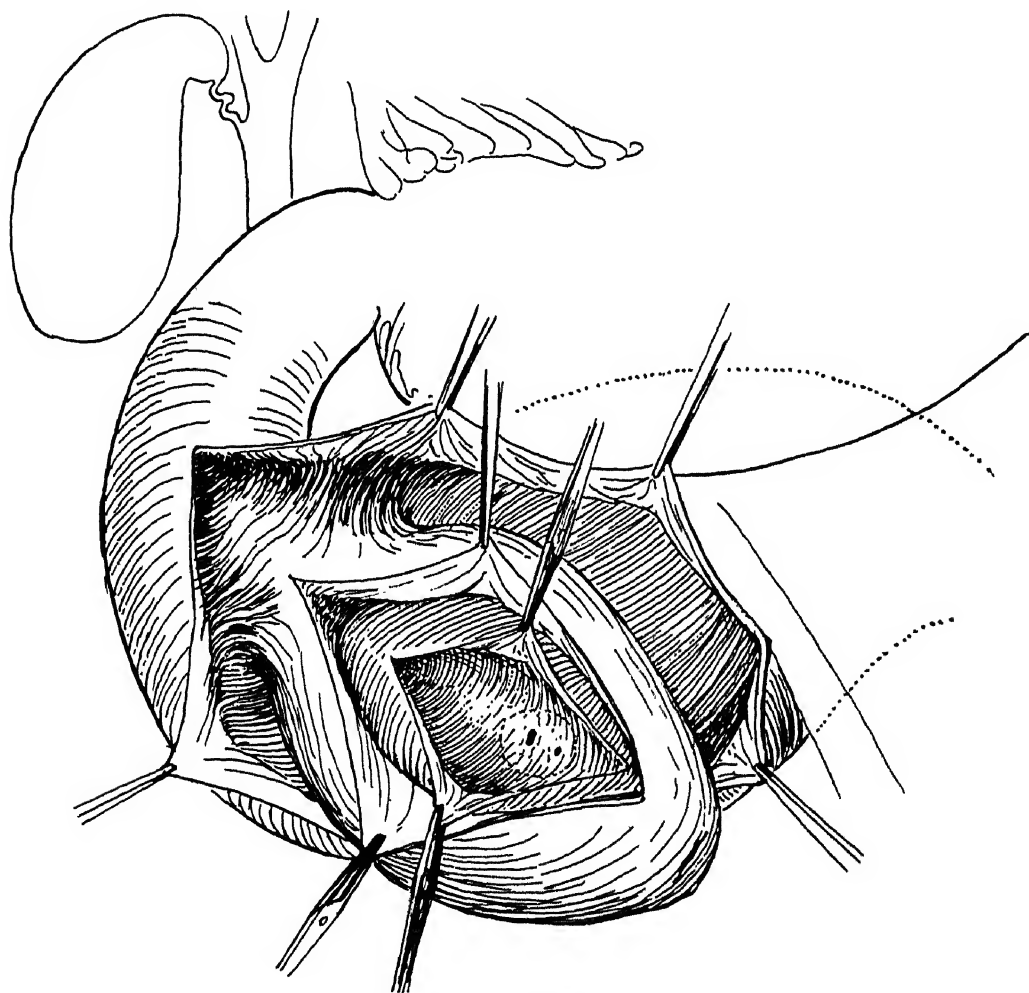


Fig. 10—Diagrammatic illustration of the appearance of the polypoid tumor after the incision was made into the central cyst. The dotted line around the apertures of the bile and pancreatic ducts marks the site of the incision made for preserving this area of mucosa for subsequent transplantation into the posterior wall. (B. Brooks and A. Weinstein: *Ann. Surg.*)

mucosa of the posterior wall of the duodenum was then closed, incorporating the island of mucosa surrounding the openings of the bile and pancreatic ducts. Gallstones were then removed from the gallbladder and a tube inserted into the gallbladder. The abdomen was

toms were explained on the basis of an *intussusception of the cyst*. The explanation for the initial anomaly is not simple; it appeared impossible to consider the cyst as having been acquired, because the slit-like opening of the cyst was larger than a normal ampulla, and the

cyst was lined with mucosa identical with the normal duodenum. It appears as if the abnormality was a congenital anomaly of the duodenal wall and not an acquired dilatation of the ampulla of Vater. The authors found no record of a similar condition with the possible exception of an "anomalous pouch" of the duodenum reported by Grant.

it was obtained by introducing a cannula with an olive-shaped tip through the stump of the cystic duct. One or 2 cm. of common duct bile was then aspirated. This procedure had the advantage of not injuring the common duct; however, it had the disadvantage of contamination by the bile from the cystic duct. In addition to the common duct bile, specimens

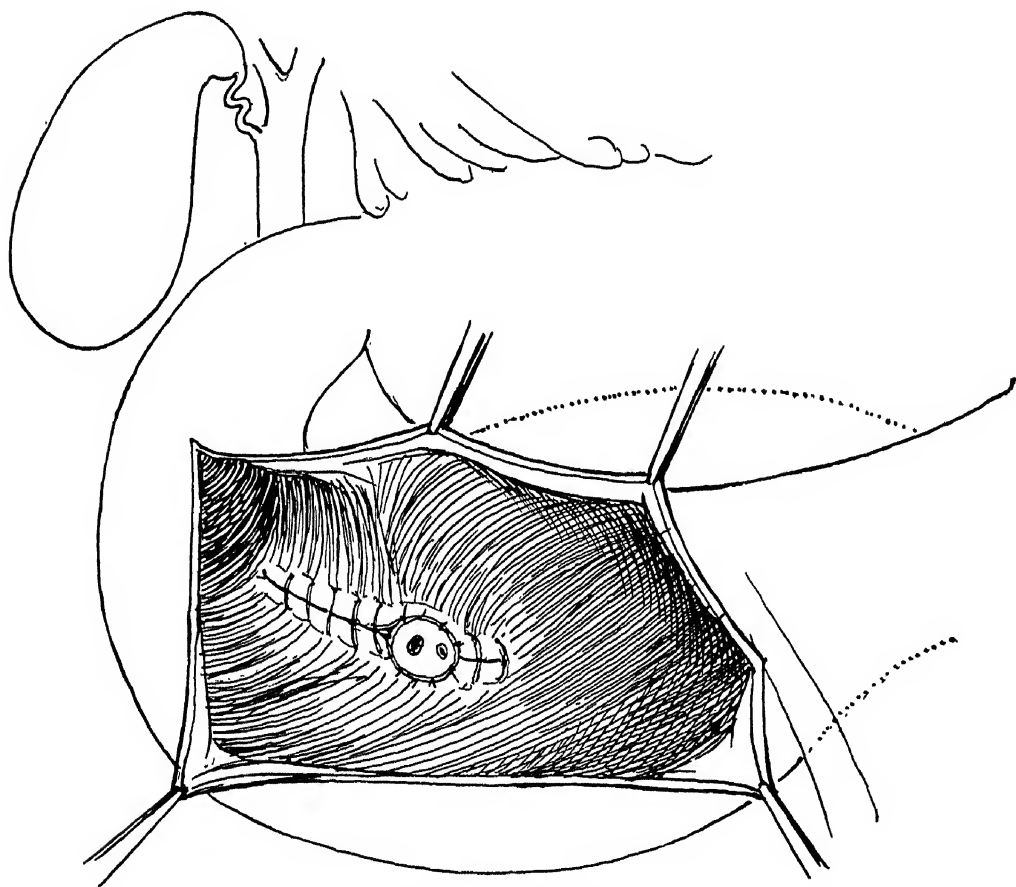


Fig. 11—Diagrammatic illustration of the method of closure of the wound in the posterior wall of duodenum containing the transplant of mucosa from the central cyst. (B. Brooks and A. Weinstein: Ann. Surg.)

### Bacteriology

A comparative study of the *bacteriology of the common duct bile*, with other extrahepatic segments of the biliary tract, was made by Elkeles and Mirizzi.<sup>5</sup> The common duct bile was removed through the wall of the duct only in cases in which choledochotomy was to be performed. In the majority of cases,

were obtained from the gallbladder and from the duodenum in all cases, as well as a piece of the wall of the gallbladder. A cystic lymph node was examined in several cases; however, it was found to be sterile and the routine study of this was discontinued.

As a result of these experiments, the following conclusions were reached:

1. *Common duct bile is sterile in a large number of patients with disease of the extrahepatic bile duct.* This occurred in 41 of the 75 cases or 54.7 per cent.

2. *Sterility of the choledochole bile* is especially frequent in cases of *uncomplicated chronic calculus cholecystitis* and *atrophic sclerosing cholecystitis*. It was observed in 25 of 34 such cases or 73.5 per cent. Since the possibility of contamination could not be excluded in seven of the ten remaining cases of uncomplicated cholecystitis in the third series, the frequency of sterile common duct bile in such cases may be about 91 per cent. The results were similar in cases of empyema, or hydrops of the gallbladder, when the gallbladder was the only organ involved by the disease. On the other hand, the choledochole bile was frequently infected when there were complications either of an organic nature, such as pericholecystitis, hepatitis, inflammation of the sphincter of Oddi, or a dyskinesia.

3. Stagnation of the choledochole bile, resulting from dyskinesia, or stenosing odditis, in the absence of stone, resulted in infection of the common duct bile in four of the seven cases. In the remaining three cases, actual infection was not observed although macroscopic alterations of the common duct bile existed.

4. Stones in the common duct were the most frequent cause of infection of the choledochole bile. Infection occurred in 16 of the 18 cases of common duct stone or 88.8 per cent. In two other cases of stone in the common duct which were found to be sterile, the explanation given was that the stone was migrating from the gallbladder to the duodenum. These cases may be associated with sterile bile in the common ducts.

5. Bacterial infection of the common duct is always associated with infection

of other parts of the biliary system and the bacteria found are generally of the same species. The predominant bacteria were *B. coli*, 72 times; streptococcus, 49 times; other bacteria were *E. typhi*, 8 times; *B. pyocyaneus*, 4 times; staphylococcus, saprophytes, and associated bacteria, 13 times. Bile in the common duct appears to have a strong bactericidal power. This finding is striking and of great practical importance.

### Perforations of the Common Duct

According to Brunschwig,<sup>6</sup> the cause of rupture of the common duct has been stated as due to one or a combination of factors which include: (a) *Increased intraluminal pressure from obstruction below the point of rupture*; (b) *necrosis of a portion of the common duct wall secondary to thrombosis of mural vessels*; (c) *necrosis of the duct wall secondary to pressure from an impacted stone*; (d) *infection*; (e) *slough of the cystic duct's stump*; (f) *rupture of a weak segment of duct wall, such as a vulnerable point resulting from common duct drainage*. The pathogenesis of rupture is obscure where there are no extensive changes in the extrahepatic biliary duct wall, and in the absence of stones. Postcholecystectomy rupture of the common duct is another unfortunate sequela of an overlooked common or hepatic duct stone at the time of cholecystectomy.

Upper abdominal pain becoming quite severe, associated with upper and later general abdominal tenderness and rigidity, elevation in temperature, marked leukocytosis, rapid pulse, varying degrees of collapse and icterus in a patient who has previously undergone cholecystectomy should strongly suggest perforation of the common bile duct with extravasation of bile and bile peritonitis. A differential diagnosis from biliary colic



due only to common duct stone or stone in the ampulla should not be difficult since the latter is not associated with peritonitis. General peritonitis and general collapse will not develop. The differential diagnosis from carcinoma of the ampulla or head of the pancreas will be readily apparent also because of the ab-

domen, and drainage of the common duct.

Cases of perforation of the common duct are presented:

1. A 67-year-old male, who had previously had a *cholecystostomy*, with removal of many stones from the gallbladder and common duct; following another attack a *cholecystectomy* and removal of a stone from a diver-

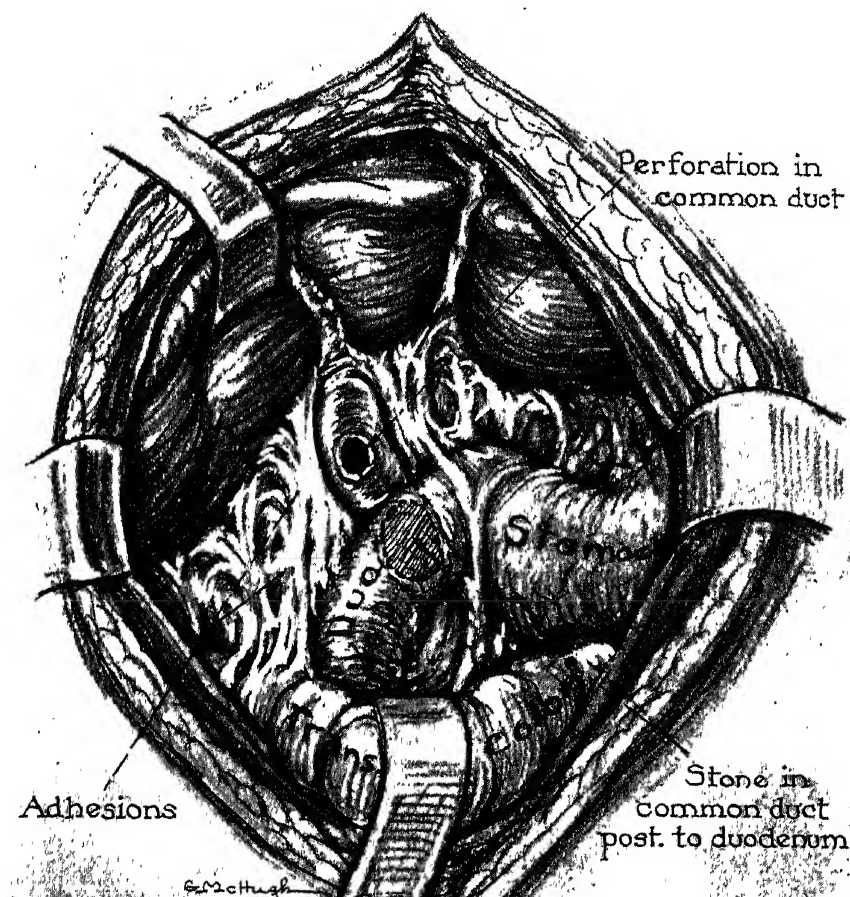


Fig. 12—Showing findings at laparotomy in Case 2. Large pocket exposed through incision of abdominal wall was filled with bile and purulent exudate; large oval perforation was present in common duct. Concretion in lower common duct was somewhat impacted in position shown. Findings suggest rupture due to hydrostatic pressure above concretion. Recovery followed stormy convalescence. (A. Brunschwig: Surgery.)

sence of evidence of peritonitis. Severe diffuse cholangitis of sudden onset might afford some early difficulty in differentiation; but, as the hours pass, lack of evidence of peritonitis will preclude the diagnosis of ruptured common duct. Due to the almost certain fatal outcome, laparotomy is indicated with evacuation of extravasated bile, drainage of the upper

ticulum of the common duct. Patient was symptom free for approximately one year, when he developed severe epigastric pain, jaundice, nausea, and vomiting. Despite supportive treatment the patient expired seven days after admission to the hospital. Necropsy revealed an acute bile peritonitis, secondary to a small perforation 1 mm. in diameter in the common duct, which was situated 3.5 cm. below the cystic duct stump. The common duct was markedly distended and a little distance below the perfora-

tion contained a single-faceted cholesterol stone, 1.4 cm. in diameter. At the level of the stone the common duct wall was thicker than elsewhere. The diverticulum of the common duct was not found.

2. A woman, 72 years of age, developed severe upper abdominal pain, nausea, and vomiting, associated with jaundice, three days prior to admission. One year previously a *cholecystectomy* was performed. *Laparotomy* disclosed a biliary peritonitis. At the bottom of the cavity, one observed a perforation in the common duct. An oval stone, 1.5 cm., was removed from the region of the ampulla. Recovery followed and the patient was well three months following operation.

Ferracani and Pages<sup>7</sup> report a perforation of the common duct by a stone:

The patient, a 45-year-old woman, was admitted with complaints of severe pains in the right hypochondrium, generalized jaundice, elevation of temperature. She had suffered from similar attacks off and on for a number of years. During the last attack she was brought to the hospital in a state of collapse. The entire abdomen was sensitive to touch, especially the right upper quadrant. Bile was obtained from a paracentesis of the posterior *cul-de-sac*. The patient expired soon after a *cholecystostomy* was performed. At autopsy, a perforation of the common duct, about the size of a penny, close to its origin was found. A calculus was kept in the opening by a diaphragm crossing the orifice. The ampulla of Vater had a normal appearance. Pathological examination disclosed inflammatory areas in the vicinity of the perforation.

Reich<sup>8</sup> discusses the causes of perforation of the bile ducts and adds *direct trauma, indirect trauma, carcinomatous invasion, and reflux of activated pancreatic enzymes* to those enumerated above. He presents a case of spontaneous rupture of a normal hepatic duct. A similar case could not be found in the literature.

The patient, a 73-year-old male, complained of severe abdominal pain of four days' duration, situated in the epigastric region, and extending backward. The pain had been continuous. He had vomited at the onset and several times since. For the past few years, he had suffered from gastric upsets and melena. Physical examination presented an abdomen

with boardlike rigidity, which was painful and tender to touch. With the diagnosis of perforated ulcer a *laparotomy* was performed. Numerous adhesions were encountered, and free peritoneal fluid of a dirty yellow color was present. This had a slightly bloody appearance near the pyloric region. No perforation of the stomach or intestines or other organs was demonstrable. Due to the poor condition of the patient further manipulation was not deemed advisable. The patient expired six hours later. At autopsy a tiny perforation was found on the anterior surface of the middle portion of the hepatic duct. There were no stones present in the biliary tract, peritoneal cavity, or intestinal tract. An atrophic cirrhosis of the liver was present.

### Carcinoma of the Cystic Duct

According to Oppenheimer,<sup>9</sup> 27 cases of *primary carcinoma of the cystic duct* have been collected from the literature. Most of these were postmortem studies and the tumor was not sufficiently localized at the time of examination to make its origin unquestionably in the cystic duct. It is pointed out that carcinoma of the extra hepatic bile ducts can occasionally be treated by radical surgery. He cites the case of Garlock, in which a small primary carcinoma of the common bile duct at the entrance of the cystic duct was resected and an end-to-end anastomosis of the common duct performed over a T-tube. This patient remained well for three years following operation. Other cases in which resection was done are cited from the literature. He presents the report of a patient who afforded an opportunity to perform a successful radical operation.

The patient was 57 years old, complaining of slight weight loss, jaundice, and light-colored stools. Examination of the abdomen showed a large smooth mass in the upper right quadrant. No evidence of radiopaque biliary calculus. An icterus index of 81 and a Vandenberg direct promptly positive. With a preoperative diagnosis of carcinoma of the head of the pancreas an *exploratory laparotomy* was performed. The liver was found to be enlarged, the gall-bladder was distended with 150 cc. of white

sterile fluid. There was an irregular mass in the region of the junction of the cystic and common ducts. The head of the pancreas was normal. The gallbladder and cystic duct and 6 cm. of the common duct were excised *en masse*. The common duct was reconstructed over a T-tube. Convalescence was uneventful. The T-tube drained well and after 43 days it was clamped off but not removed. After seven months the patient began to show anorexia, abdominal pain,

### Cholangiography

Bettman, *et al.*,<sup>10</sup> point out that one of the chief problems of gallbladder surgery has to do with exploration of the common duct. If stones are present in this duct, it is desirable to remove all of them; if no stones are present, it is best to leave it alone. The indications for exploration of the common duct have

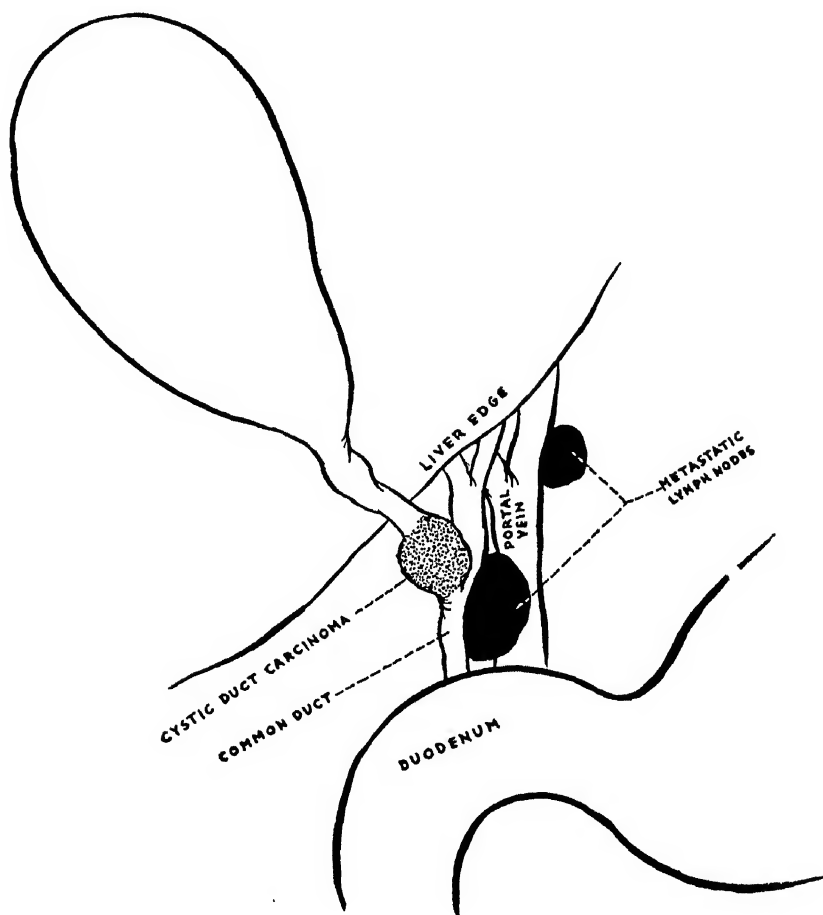


Fig. 13—Diagram illustrating findings at operation. (G. D. Oppenheimer: *Ann. Surg.*)

progressive weakness, and liver enlargement. He died 11 months following operation. There was no postmortem examination. The periportal lymph nodes showed metastases at operation.

The prolonged excellent palliative results in this case were probably enhanced by leaving the T-tube in place so that it acted as a safety valve by preventing obstruction from local recurrence or scar formation.

been: (1) A patient jaundiced at the time of operation, or having a history of jaundice; (2) palpable stones in the common duct; (3) dilated common duct.

In 500 cholecystectomies, the common duct was opened 45 times. In about one-third of the cases, no stones were found. The possibility of overlooking a stone by probing or palpation is emphasized, and for this reason the procedure

of operative cholangiography has been adopted by some surgeons. The technic employed is as follows:

A portable x-ray machine, which is sparkproof and has no high tension cables exposed, is brought into the operating room. A small Buckey diaphragm



Fig. 14—Actual immediate cholangiogram showing three radiolucent stones. Note the cystic duct through which, in this case, the common duct was injected; the common duct is slightly dilated. Note the spill into the duodenum through the patent ampulla of Vater. For the sake of clearness the upper part of the film showing the branching of the hepatic radicals of the biliary tree is not shown. (R. B. Bettman, W. J. Tannenbaum, and R. A. Arens: Surgery.)

with a tunnel for the plate is placed on the operating table. The diaphragm is so placed that its center will underlie the site of the patient's common duct. The actual surgical procedure is performed in such a manner that all bleeding points are ligated, and the hemostats are removed from the field before the

cholangiogram is taken. Laparotomy towels are sutured to the skin. The cystic duct is isolated and a ligature passed around it. A small slit is made into the duct and a ureteral catheter is threaded into the cystic duct and through it into the common duct. The ligature is then tied with a single knot around the cystic duct just proximal to the opening, tightly enough to hold the catheter in place. From 5 to 20 cc. of a sterile solution of skiodan and acacia are injected through the catheter into the duct. The operative field is covered with a sterile towel. The machine is wheeled into place and the picture is taken.

It is possible to detect the presence of stones and to differentiate them from air bubbles in the common duct. Likewise it is possible to differentiate edema of the ampulla of Vater from stenosis. In cases of multiple stones, cholangiography has been very helpful to the surgeon in enabling him to obtain from the common duct the same number of stones which are visible through the x-ray. The authors believe that within the next few years the procedure will be universally adopted.

Due to the possibility of overlooking stones in the common duct, even in cases where the common duct has been explored and a T-tube has been left in for drainage, it is important to do a cholangiogram before removing the T-tube. Clute and Lawrence<sup>11</sup> routinely follow this procedure. They report four recent postoperative cholangiograms where a filling defect in the common duct, close to the lower end of the T-tube, was found. It was suggestive of a residual stone, but on further study each case was found to be due to an artifact. Stones were not found at operation in any of these cases. Further investigation revealed a clot of old blood, bile, and mu-

cus clinging to the lower end of the T-tube to be the cause of the defect in three cases, as demonstrated on removal of the tube. In one of the cases a cholangiogram demonstrated a diminution in the size of the filling defect over several days, probably as a result of the mechanical irrigation of the tube. The clot did not obstruct the flow of bile in any of the cases.

Study of the cholangiogram of these cases showed the following findings to be of value in differentiating such partial obstructions from stones or other solid foreign bodies in the common duct: The *filling defects appeared in direct or nearly direct contact with the lower end of the T-tube*; the defect changed in shape in serial roentgenograms because of the malleability of the soft clot by the action of the bile current, of the injected radiopaque medium, or of the local duct contraction or relaxation; stringlike defects extending from the principal filling defects several centimeters distally in the duct; irrigation through the T-tube with the injection of opaque medium apparently washed out part or all of the clot from its attachment to the tube, and that changed the appearance of the filling defect on subsequent films. A typical case illustrating such findings is reported in detail. Consideration is also given to the fact that *air bubbles present in the common duct may simulate a smooth oval residual stone*. One case in which this was true is cited and illustrated by roentgenograms. These cases can usually be differentiated by the fact that the shadows change in size and shape on serial films, and also because of evidence of air around the arms of the T-tube.

Two cases of common duct calculus in which stones remained in the duct after operation were reported by Morton.<sup>12</sup> In each case the stone was disintegrated by the action of ether and al-

cohol injected into the T-tube. This dissolution of the stone and its passage into the duodenum were demonstrated by cholangiographic studies. The first case was complicated by postoperative hemorrhage, there were no stones demonstrated in the gallbladder or the common duct at the primary operation, and its shadow interpreted as a stone was at the lower end of the tube. Following irrigations with one-third ethyl-alcohol and two-thirds ethyl-ether in amounts of 5 cc. for five days through the T-tube, a cholangiogram failed to show evidence of stone. These factors suggest the possibility of an artifact as described by Clute and Lawrence. The second case showed stones in the gallbladder and the common duct at the time of primary operation, and the possibility of a stone in the common duct, which was overlooked, is more definitely suggested. Injections of the ether-alcohol mixture reestablished biliary continuity with the intestinal tract, and cholangiograms demonstrated prompt and free discharge of the medium from the common duct into the duodenum, and failed to show any stone or other obstruction.

### Choledocholithiasis

An overlooked stone in the common duct is known to all as a cause of persistent symptoms following cholecystectomy. Considerable dispute exists regarding the indication for exploration of the common duct. Most authorities are agreed on these indications for exploring the common duct: (1) Jaundice at present, or jaundice in the past; (2) dilatation of the common duct at operation; (3) palpation of a stone in the common duct at operation. To these indications may be added the following: (1) When the head of the pancreas is thickened; (2) when the gallbladder is thickened and contracted; (3) when the aspirated

common bile duct contains dark, cloudy, murky bile; (4) the presence of infection in the common duct.

In an analysis of 2602 cases of biliary tract disease, O'Shea<sup>13</sup> reports that 1204 had stones. Four per cent had stones in the extrahepatic biliary duct; 95 of the calculi were in the common ducts, and in six patients stones were found in the hepatic duct. There were cases in which the obstruction was caused by the *strongyloides stercoralis*. Common duct stones were found in 6.2 per cent of all the operative cases, whereas the ducts were drained in 7.7 per cent of the cases.

According to Hooker,<sup>14</sup> 165 choledochotomies with exploration of the common bile duct were performed during the same period that 2117 cholecystectomies were performed. Therefore, approximately 13 cholecystectomies and one choledochotomy were performed. Of the 165 cases, 114 or 69 per cent were female. Over one-half of the cases were in the fifth and sixth decades of life. Pain, nausea, vomiting, and eructations of gas were the commonest symptoms. Pain was usually located in the epigastrium somewhat to the right side. In many cases the symptoms date back two to three years, and the acute attack was usually of less than one week's duration. Sixty-four of the 165 patients complained of chills and fever. Clinical jaundice showed in 122 cases, while the icterus index was elevated in over one-half of the 165 cases. In the majority, the icterus index was not above 50. There were 120 cases completely cured, five required another operation, and 22 died, total mortality in this series being 9 per cent. Exploration of the common duct definitely carries a higher mortality and should be done only for specific indications.

Milbourn<sup>15</sup> studied 284 cases of stones in the common duct occurring in a 15-

year interval. The diagnosis was verified at operation in 196 by passages of the stone per annum in 67 and at autopsy in 27. It was noted that early in the biliary attack the blood icterus values may be elevated without icteric discoloration of the skin, and late in the attack, the discoloration outlasts the elevated blood pigment value. The Muelengracht method—a direct colorimetric reading of the intensity of bile pigment in the blood serum—was more exact than the Vandenberg test. Extensive studies of the urinary diastase were done. The method consisted essentially in determining, by means of iodine-K. I. solution as the indicator, the point of complete digestion of starch solution by a series of graded concentrations of the patient's urine in salt solution. In an attempt to evaluate the significance of elevated urinary diastase, in detecting the presence of stone in the common duct, 263 of the 284 patients known to have had a choledochus stone, whose urinary diastase had been more or less thoroughly observed, were selected. Among these 263 was a group of 191 patients who exhibited icterus during their hospital stay of whom 82 (43 per cent) also showed an elevation of their urinary diastase and a group of 72 patients who did not exhibit icterus during this time, of whom 17 (24 per cent) also showed elevation of the urinary diastase. The author felt that an elevation of urinary diastase, as an isolated symptom indicating stone in the common duct, is not as constant or dependable as has often been presumed in the past.

The relationship existing between increased urinary diastase, and the presence of pancreatic complications in biliary tract disease, is similar to that found by other authors. Of the 263 patients, 104 (40 per cent) whose urinary diastase was subject to study, proved to have a



pancreatic complication. The diagnosis was unequivocal in 25, in 15 it was probable, while in the remaining 64 the acute pancreatic affection was probably induced by a mild transient reflux or stasis in the pancreatic duct, arising from direct obstruction to the outflow of bile and pancreatic secretion into the duodenum by the incarceration of a stone in the opening, or from a reflex spasm of the sphincter of Oddi. The stasis in the pancreatic duct was not of sufficient degree or duration to produce gross anatomical damage of the pancreas. These studies bear out the view of Skoog that the degree of elevation of urinary diastase does not parallel the severity of the pancreatic involvement. In the more severe types of pancreatic disease, the elevation of urinary diastase was only moderate. Even in those cases of biliary attack, in which no elevation of diastase values is detected, the possibility of acute pancreatic complication is not excluded, as the elevated values tend to return to normal rather quickly—less quickly when the pancreatic involvement caused gross anatomical changes. Postoperative studies of urinary diastase were conducted on 124 patients who had been choledochotomized, and elevated values were found in 28 (23 per cent). In 19 (15 per cent) the rise occurred immediately following operation. It was suggested that in some instances this increase following operation may have been carried over from the preoperative state, and in other cases operative trauma may have been the precipitating factor. An elevation of the diastase value late in the postoperative period suggested a stone or stones in the common duct overlooked at the time of operation. Search of the stool, during the postoperative period, may reveal a stone which was overlooked at operation and passed in the postoperative period.

In 15 per cent of the patients who had biliary symptoms following choledocholithotomy it was practically certain that the trouble was due to concretion overlooked at operation and in 14 per cent it was probably due to that cause. None of the stones which were passed were thought to have reformed since the operation. In order to avoid overlooking stones at the time of choledocholithotomy the author suggests cholangiography during operation and even a controlled cholangiogram before the end of the operation, in order to avoid leaving stones within the common duct, which is the most common cause of persistent symptoms following operation.

### **Reconstruction of the Common Duct with a Vitallium Tube**

An interesting case of stenosing stricture due to fibrosis of the common duct following a simple cholecystectomy, in which biliary continuity was reestablished by means of a vitallium tube after four operations, is presented by Carlucci.<sup>16</sup> The case history is that of a 30-year-old male who was operated upon in 1940 for chronic cholecystitis and cholelithiasis, a simple cholecystectomy being performed. One week postoperatively, acute jaundice developed and the patient was reoperated, a T-tube being placed in the common duct for over eight weeks. He was well until January of 1941, when the jaundice recurred, and an external biliary fistula was established in February, 1941. In May, 1941, he was readmitted because the biliary fistula had closed. He was discharged after reestablishing the external biliary fistula by catheter. In June, 1941, the biliary fistula was implanted into the prepyloric end of the stomach. Following this, recurrent attacks of jaundice and fever followed. The patient was operated upon again in October, 1941. At this time the





Fig. 15—The vitallium tube has been inserted into the stump of the common hepatic duct, being held in place with silk sutures. The distal portion of the common duct has been freed. (H. M. Clute: New England J. Med.)



Fig. 16—The vitallium tube has been placed in the common duct. It should be noted that a portion of the duct is completely lacking. Convenient fat tabs and omentum were used to cover the exposed tube. (H. M. Clute: New England J. Med.)



Fig. 17—This x-ray film, taken some months postoperatively, shows the vitallium tube in the common bile duct and its relation to the barium-filled stomach. (H. M. Clute: Internat. Ab. Surg.)

external biliary fistula was reestablished. In February, 1942, a 4 cm. vitallium tube was inserted into what was left of the common duct. This was placed in the prepyloric end of the stomach. The patient has remained free of symptoms for nine months since this last operation.

A case in which successful reconstruction of the common duct was performed is reported by Clute.<sup>17</sup> A woman aged 38 had a cholecystectomy performed for gallstones 16 months prior to her first admission to his care. At this first operation hemorrhage from the cystic artery made it necessary to place a clamp, which apparently produced a stricture of the common bile duct. Four months after this, she was operated upon for the second time, the diagnosis being inoperable stricture of the ducts. The third operation in July, 1939, consisted of placing a T-tube in the strictured common duct. The patient remained well until the tube was accidentally pulled out. A fourth operation in April, 1940, consisting of hepaticoduodenostomy, resulted in recurrent symptoms of pain, chills, fever, and jaundice after six months. A fifth operation in November, 1940, consisted of liberation of the duodenum with closure, removal of gallstones from the common duct, which remained, and the insertion of a trumpet shaped vitallium tube held by silk sutures to the liver. The distal end of the tube was placed in the distal portion of the common duct, omentum was brought around the tube. Recovery was uneventful and the patient was entirely well for six months. She then had a transient attack of pain and jaundice. X-ray examination at this time showed no change in the position of the tube. Patient remained well when last seen August, 1942.

By means of a free fascial graft from the anterior sheath, fashioned into a

cup around a straight vitallium tube as a holder, a gap in the common duct of a dog can be bridged with uniform success according to Lord and Chenoweth.<sup>18</sup> Venous grafts were only moderately successful. Free peritoneal grafts should not be employed since these sloughed in four of the five cases.

**Complications** — Consales<sup>19</sup> reports a case in which a rubber tube was retained for 4½ years in a choledochoduodenostomy communication without any untoward symptoms, and expulsion of the tube and complete restoration of the biliary-duodenal continuity eventually occurred. The horizontal part of a T-tube had broken off at the time of removal and became an indwelling rubber tube. It was retained within the biliary-duodenal anastomosis without any complications for the 4½ years. In such operations, the use of the new T-tube constructed in one piece is recommended.

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## BILIARY SYSTEM

FREDERICK A. FISKE, B.S., M.D., F.A.C.S.

## Physiology and Pharmacology

As a result of experimental studies on dogs, Svien and Mann<sup>1</sup> conclude that distention of the gallbladder, through a pressure range from 20 to 400 mm. of mercury, does not produce any change in the activity of either the upper jejunal segment or the lower ileal segment of the small intestine. They have shown that distention of the upper part of the urinary tract produces an inhibition of activity of the jejunum and the ileum, which persists in most instances as long as the distention is maintained, and in some instances for variable periods up to five minutes after the distention of the upper part of the urinary tract has been released. These studies offer a possible explanation for the reflex gastrointestinal symptoms noted clinically in cases in which there are proved disturbances of the upper urinary tract.

Canonico and Mann<sup>2</sup> investigated the intestinal activities before and after ligation of the common bile duct, using methods which permitted observation and recording of activity of loops of intestines under as nearly normal conditions as they were able to devise. As a result of these studies, it was found that obstruction of the common bile duct was followed by marked decrease of activity in exteriorized loops of jejunum and ileum during the first two weeks after operation. Subsequently, intestinal activity increased, but never equaled the normal amount in jaundiced animals. The decrease of intestinal activity occurred in both the fasting and digesting states but was more noticeable in the latter. It is suggested that the biliary constituents retained in the blood, particularly the bile salts, may be of importance in caus-

ing the observed alteration of intestinal activity.

Boyden *et al.*<sup>3</sup> studied the effect of *magnesium sulfate* on the gallbladder in a group of medical students in order to make comparisons with the sphincter studies significant. It was found that: (1) Magnesium sulfate is an effective agent in evacuating the human bile tract, but is inferior in this respect to egg yolk. Thirty cubic centimeters of a saturated solution introduced directly into the duodenum induces, within 30 minutes, an average decrease of 42 per cent in the volume of the gallbladder and lowers the sphincter resistance 3 cm. of water. In the same interval egg yolk lowers the gallbladder volume 71 per cent and the sphincter resistance 7 cm. (2) Magnesium sulfate acts upon the gallbladder and upon sphincter in the same way and for the same length of time as egg yolk. It differs only in degree, a characteristic which may be attributed to the slower absorption rate for the less effective chemical acts. Accordingly, it is suggested that magnesium sulfate, like egg yolk, is to be considered as a hormone-producing substance which acts independently, through the blood stream, upon both the gallbladder and the sphincter of Oddi. (3) The two end organs react differently to a given stimulus; initially a dose of either egg yolk or magnesium sulfate usually causes the sphincter to contract. This in turn may interrupt the contraction of the gallbladder which is just getting under way, thereby producing the so-called "two-minute phase." By the end of the first four to five minutes, however, the sphincter enters a period of progressive relaxation which lasts for an average period

of 17 minutes. Meanwhile, the gallbladder begins its main phase of contraction which lasts for an average of 30 minutes. Evidence from animal experimentation suggests that the reason why the hormone acts upon the sphincter for a shorter time than upon the gallbladder is that during fasting the tone of the sphincter is maintained by a local nerve net, which has a higher threshold than that of the gallbladder.

celiac division produces even greater retardation of flow, from which it is inferred that the right vagus not only sends parasympathetic inhibitory fibers to the sphincter region *via* the gastroduodenal nerve, but also motor fibers to the gallbladder *via* the hepatic plexus. The latter interference is substantiated by the fact that severance of the left vagus (which does not send fibers to the choledochoduodenal junction) also retards

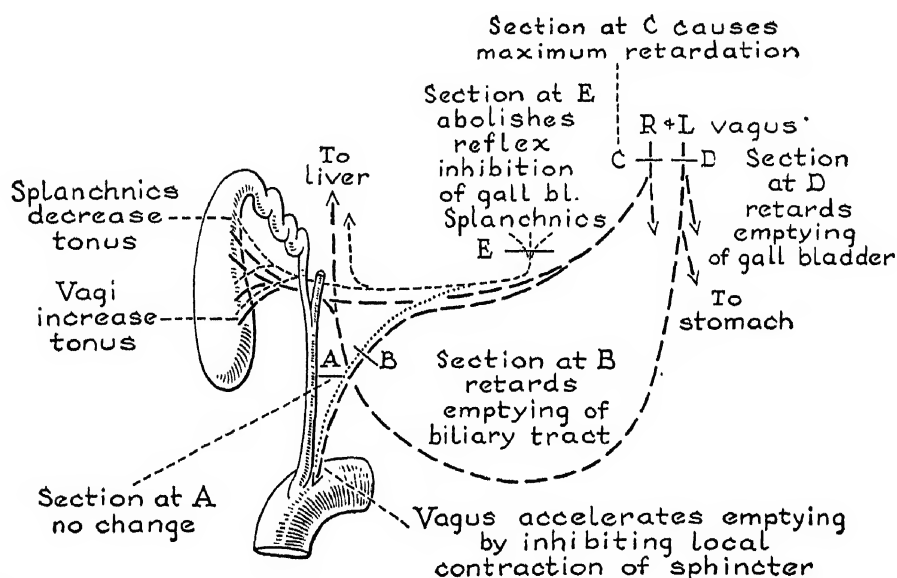


Fig. 1—Diagram summarizing the effects of sectioning various autonomic nerves. Area A, gastroduodenal plexus; B, gastroduodenal nerve. (F. E. Johnson and E. A. Boyden: Surg., Gynec. and Obst.)

The effects of cutting or otherwise eliminating certain nervous pathways to the biliary tract in 34 cats is represented in Fig. 1, as reported by Johnson *et al.*<sup>4</sup> These effects are summarized as follows: Severance of the gastroduodenal plexus to the choledochoduodenal junction does not affect the rate of emptying of the bile passages after ingestion of food, nor abolish the inhibitory reflex to the gallbladder from the cecum. Presumably, this plexus consists of afferent and vasomotor fibers. Severance of the gastroduodenal nerve, which innervates the same junction, markedly retards emptying. Severance of the right vagus and its

the emptying of the gallbladder, but to a lesser degree.

Severance of the splanchnic routes of the celiac ganglion, as far down as the second lumbar nerve, abolishes the inhibitory reflex from the cecum to the gallbladder, thereby somewhat accelerating the emptying of the gallbladder. It is suggested, therefore, that during fasting the biliary outlet is closed through the action of a local mechanism, perhaps the intrinsic nerve net, and that after meals the tonic contraction of the sphincter is overcome by the right vagus and by the hormones being formed in the intestinal mucosa. Since in human patients the

neuromimetic drugs have so little effect upon the spastic sphincter, it is possible that in man the vagus has lost its power to release the sphincter and that this is accomplished only by antispasmodic and hormone-producing substances.

These experiments also indicate that in part there is no obligatory reciprocal relationship between gallbladder and sphincter, since each responds to appropriate stimuli when the nerve to the other is cut. The vagus augments the tone of the gallbladder and inhibits contraction of the sphincter (thereby accelerating the flow of bile); the sympathetic exerts a temporary inhibiting effect on contraction of the gallbladder—a function that is apparently absent in man—thereby retarding the flow of bile from a viscus that is emptying under the influence of hormones and emanations from the vagus.

Pain impulses from faradically induced spasms of the cecum enter the spinal cord as low as the second lumbar ganglion, having traversed the superior mesentery plexus and the last splanchnic nerve.

Lynn *et al.*<sup>5</sup> conducted an experiment on dogs with ligated cystic ducts showing that *sulfanilamide*, *sulfathiazole*, and *sulfadiazine* do not enter the gallbladder when the cystic duct is occluded. The sulfones do not pass through the wall of the vesicle to reach the gallbladder bile. While it has been shown that the sulfonamides are excreted in man, and certain laboratory animals, in the bile and there is clinical evidence that these drugs exert a beneficial effect in some biliary infections, on the other hand, in many cases of biliary disease there is no benefit from the drug. This may be explained on the basis of an occluded duct as demonstrated in these experiments.

Bergh and Layne<sup>6</sup> studied the effects of magnesium sulfate on the sphincter of Oddi in patients who had previously undergone cholecystectomies, choledochotomies, and intubation of the common duct. *Magnesium sulfate* was given in doses of 12.5 Gm. dissolved in 30 cc. of water and administered either by mouth or by duodenal tube. The conclusions reached were that *magnesium sulfate may produce any one of four types of effects on the sphincter of the common bile duct*. It may produce relaxation with or without an initial contraction. It may produce an initial contraction followed by a return to the original tonus level, or there may be no effect. Equal relaxation was noted regardless of the method of administering magnesium sulfate. The relaxation, however, is not constant and is considerably less than that following the administration of amyl nitrite or the ingestion of a fatty meal.

The problem of biliary dyskinesia was studied by Long.<sup>7</sup> The anatomy and applied physiology of the common duct at its opening into the duodenum was surveyed. Although anatomically an independent "sphincter of Oddi" is demonstrable, yet physiologically the presence of an independently active sphincter has never been shown conclusively. It has been difficult to differentiate the action of the sphincter from the effect of a strongly active duodenal wall.

On a series of 53 dogs, it was shown that the choledochosphincter and the muscular coat of the duodenal wall usually contract together. On the other hand, it was shown that the choledochosphincter can act independently of the activity of the duodenal wall, from the physiological standpoint.

To discover the stimulus which may be responsible for the independent action of the sphincter, Long designed a simple apparatus for perfusing fluid

through the common bile duct into the duodenum and for measuring the resistance offered to the flow of fluid by the choledochoduodenal mechanism. The tracing of a normal dog is presented and the effects of administering *morphine* in considerable doses is recorded. Tracings are likewise given showing the effects of antispasmodic drugs, such as *atropine* and *syntropan*, after the subcutaneous injection of morphine. Studies of *amyl nitrite*, *sodium nitrite*, introduced into the stomach and into the perfusing fluid, as likewise of minimal doses of *acetylcholine with adrenalin* were also made. Finally, the effects of introducing bile into the perfusing fluid and the importance of the pH of the bile and the concentration of bile salts in relation to the working of the choledochosphincter were demonstrated.

The conclusion is drawn that biliary dyskinesia is merely one manifestation of the earliest stage of changes that occur because of back pressure of bile in the biliary tract. Pain from spasm of the sphincter, which will not allow the strongly contracting gallbladder to empty itself, results. Nausea and vomiting follow the distention of the biliary passage, and there is a temporary decrease in the production and output of bile salts either concomitant with or following a temporary derangement of the liver. The same sequence may occur after cholecystectomy.

### Gallbladder

**Etiology** — Biebl<sup>8</sup> observed three cases of *biliary disorders which had occurred in connection with trauma*.

A railroad worker, aged 22, was thrown against a crank, the impact striking the epigastric region. He experienced immediately a severe pain in the gastric region, which was intensified on motion and on deep breathing. Pain radiated towards the right scapula. The patient later collapsed and was brought to the

hospital. Laparotomy disclosed that the gallbladder was torn away from the liver bed. The gallbladder was removed.

The second patient was a man, aged 54, who had fallen from a bicycle. At operation two days later there was found peritonitis, caused by tears in the small intestines. An intestinal resection was performed. Three weeks later the patient was subjected to a cholecystectomy because of symptoms of acute cholecystitis. The removed gallbladder presented a circumscribed mucosal tear in the fundus of the gallbladder. The wall in the region of the tear was necrotic; perforation did not take place. Colon bacilli apparently had entered the gallbladder and had caused a cholecystitis.

The third patient was a man, aged 52, who had an automobile accident and sustained a patella fracture. He was unaware of any abdominal trauma. Five weeks after the accident acute cholecystitis suddenly developed. The gallbladder contained two calculi. The wall in the region of the body was found to contain numerous intramural abscesses. In the region of the fundus there was an inflamed mucosal flap, and a portion of the wall was denuded of mucosa. It is suggested that streptococci, which produced the mural abscesses, had found a breeding place under the torn-off mucosal flap and that the postoperative suppuration of the knee was probably a hematogenous result of cholecystitis.

The mucosal lesions in cases 2 and 3 were probably caused by trauma. Resulting cholecystitis therefore may be designated as "*traumatic cholecystitis*."

During some nutritional experiments Okey<sup>9</sup> added 25 mg. of riboflavin and 125 mg. of calcium pantothenate to the diets of some pigs. The guinea pigs, which were fed cholesterol and given supplementary vitamin B, showed an abrupt and usually fatal anemia without the usual preliminary loss of weight or other signs of illness. Eighty per cent of the necropsies in these fatal cases revealed gallstones, accompanied by irritating lesions of the gallbladder and biliary passages. The control animals fed on cholesterol without vitamin B did not show gallstones. Okey found that all previously recorded cases of gallstones

were associated with diets particularly rich in cholesterol (unextracted casein and/or egg yolk) and diets also probably containing an excess of riboflavin. The conclusion seems to be that *an overabundance of vitamin B will lead to gallstone formation in animals otherwise tolerant to cholesterol-rich diet*. The gallstones were rich in calcium phosphate, although containing some cholesterol.

An analysis of the literature and reports of *two unusual cases of extrapulmonary Klebsiella pneumoniae* (Friedländer's bacillus infections) were reported by Jaffe.<sup>10</sup> It was pointed out that, contrary to the usual conception, the majority of infections are primary in sites other than the lungs and respiratory tract. The primary sites of infection in 198 cases recorded in the literature were: Gastrointestinal tract, 61; biliary passages and liver, 46, thus accounting for 54 per cent of the total infections. Stasis in the biliary or urinary tract due to stones, neoplasm, or external pressure plays a definite rôle in predisposing to infections in these regions.

The first case reported was one of primary infection in the ankle, which necessitated amputation of the leg; recovery followed the use of sulfadiazine locally and systemically.

The second case was a 39-year-old housewife, who had a typical history and physical manifestations of an acute exacerbation of chronic cholecystitis with cholelithiasis. A gangrenous gallbladder containing stones was removed on the sixth hospital day. Within 24 hours after operation she developed respiratory distress, cyanosis, and a spiking temperature from 100° to 104° F. The stormy septic course continued for three weeks. At this time a subphrenic abscess was suspected and a thoracotomy was done through the eighth interspace at the posterior axillary line. Aspiration of pus through the diaphragm yielded a pure culture of *Klebsiella pneumoniae*. **Sulfanilamide** therapy was started and several days later a mushroom catheter was inserted through the diaphragm. Drainage was profuse for the first two days.

This was positive for Friedländer's organisms. During the next three weeks she was kept on a régime of sulfanilamide therapy and **small transfusions**. She was discharged in eight weeks from the time of admission. The thoracotomy healed spontaneously within five weeks after discharge. Five years after the operation she is still well, complaining only of mild dyspnea on moderate exertion.

From 5698 autopsies, Kinney and Ginsberg<sup>11</sup> found 52 cases of liver abscess of all types, a general incidence of 0.9 per cent. Bacteriological studies were carried out in 30 cases and *Friedländer's bacillus was identified in seven, or 23 per cent*. There was no single sign or symptom found which would distinguish liver abscesses due to Friedländer's bacillus from those in which the usual pyogenic organisms were the etiological agents. Blood culture was the only positive laboratory finding of value. The gross appearance of the liver abscess was the same as that of other abscesses caused by pyogenic organisms, with the exception of the exudate. *Multiple abscesses were present in all but one case. The exudate was characteristically glairy and mucoid*. It was similar in all respects to that seen with Friedländer's bacillus infections in other parts of the body. Microscopically, there was nothing to distinguish these abscesses from other pyogenic liver abscesses except finding the organism. Disease of the biliary system, other than that of the liver, was present in four of the seven cases presented: In one case, a definite obstruction of the common bile duct; in another, acute suppurative cholecystitis and cholelithiasis, acute suppurative pancreatitis, early adenocarcinoma of the head of the pancreas, and acute pylephlebitis were present. The third case was associated with acute empyema of the gallbladder and cholelithiasis, but no infection of any of the hepatic ducts. The fourth case was associated with chronic



cholecystitis and cholelithiasis. In one case the abscess resulted from direct extension from the stomach. They also emphasize the fact that the bacillus has been found producing lesions in practically every organ of the body and it is normally found in the gastrointestinal tract.

Rubenstein<sup>12</sup> points out that *acute cholecystitis* may be of *typhoid origin*. Due to the relative infrequency of typhoid and its complications, one rarely thinks of this disease when confronted with a case of acute cholecystitis. Four cases of acute cholecystitis are reported to re-emphasize the importance of this complication. Two of the four cases came to operation before the association with typhoid had been established. In two instances, secondary attacks occurred among the personnel of the hospitals to which the patients had been referred for operative procedures.

In the first case, that of a 25-year-old physician, a diagnosis of typhoid fever was made, and during the convalescent period an attack of acute cholecystitis developed. This subsided spontaneously.

The second case was a housewife, aged 28, admitted to the hospital with acute pain in the upper right quadrant, of one day's duration. For three weeks before admission a severe infection of the upper respiratory tract, associated with heaviness of the chest and a productive cough, had been present. About one week later fatigue developed. One day after admission to the hospital the gallbladder was removed under spinal anesthesia. It was tense, edematous, and inflamed, with several small areas of necrosis. No stones were present. The postoperative course was complicated by a spiking temperature, which gradually subsided within 15 days, at which time she was discharged from the hospital. Six weeks after the operation the Widal reaction was found to be positive and typhoid bacilli were recovered from the stool.

The third case, of a 29-year-old female, admitted with the chief complaint of upper right quadrant pain of two days' duration, with a history of malaise, headache, fever, for two weeks preceding the onset of this attack. Physi-

cal findings were limited to the abdomen, which showed spasm, tenderness in the upper right quadrant, with a nonpalpable gallbladder. A leukocytosis of 25,500 was present. Operation was performed one day after admission. A large distended gallbladder was found matted down to the liver bed by adhesions. The liver was slightly enlarged. A cholecystotomy was performed. Following operation the temperature remained elevated, spiking between 99° and 103° F., for ten days. It then gradually subsided and became normal 17 days after admission, and 28 days after the onset of her illness. Stool cultures remained positive for one year following this illness. The patient was listed as a typhoid carrier. A cholecystectomy was performed to correct this condition.

Case 4, a female, aged 29, was admitted with a history of cough, headache, and fever of five days' duration. One month after admission, she was operated upon for an acute cholecystitis, which developed in the course of typhoid infection. The gallbladder was drained. *Eberthella typhosa* was cultured from the bile at the time of operation. Following operation, the stool cultures and drainage from the biliary fistula were consistently positive for *E. typhosa*. One year later a cholecystectomy was performed to relieve the carrier state.

It is pointed out that acute cholecystitis as a complication of typhoid may appear during the course of the disease or early in convalescence. Any case of acute cholecystitis, in which the onset of the gallbladder symptoms is preceded by a bout of unexplained fever, should be studied as a possible case of typhoid. Chronic cholecystitis is a frequent result of the localization of the typhoid bacillus in the gallbladder of typhoid carriers. Every patient with gallbladder disease who has a definite or suggestive history of typhoid should be placed on typhoid precautions until laboratory study excludes the carrier state. These measures will prevent possible infection of hospital personnel from contact with patients with undiagnosed typhoid and with unrecognized typhoid carriers. Routine immunization of hospital personnel against typhoid will also minimize the hazard.

According to Collier and Crabtree,<sup>13</sup> typhoid carriers are much more prevalent than is generally realized. The four places where typhoid bacilli may remain and give rise to the carrier state are: Hepatic, urinary, intestinal, and gallbladder. The hepatic, urinary, and intestinal carriers are rare. However, many patients harbor the organism in their gallbladder and thus have positive stools for as long as six to eight months after the attacks. The methods of treating typhoid carriers have been surgical and medical. Cholecystostomy and cholecystectomy have been done to effect this cure, the latter being the most generally accepted means of curing the carrier state. Conservative measures which have been tried include deep roentgen therapy over the gallbladder, a prolonged course of drainage by means of a duodenal tube, and the use of drugs. The criteria for performance of operation upon chronic biliary typhoid carriers are that the person must be a chronic carrier, a bile carrier, and a good surgical risk. After cholecystectomy, release may be made if 12 consecutive fecal specimens, obtained at monthly intervals, are negative, and one bile specimen obtained during the year following the operation is negative. Studies of 21 new chronic biliary typhoid carriers were made. Operation was performed primarily for a cure of the carrier state, although gallbladder disease was present in 11 of the 21 cases. Sixteen of the patients in the series were cured, although released bile specimens have not been obtained from all of them. Three cases are too recent for a positive cure, but in time they will probably be so classified. If these patients are excluded the percentage of cure is 88.9 per cent. There were no fatalities in the 21 cases.

**Pathology**—Golob and Kantor<sup>14</sup> present two cases of *double gallbladder* in order to point out that this condition

may confuse the clinical picture of gallbladder disease. In both cases double gallbladders were detected in routine roentgenographic studies, although no symptoms referable to gallbladder disease were elicited. In the first case, one of the gallbladders contained stones. It is pointed out that if the condition is not proved by cholecystography the accessory gallbladder may be overlooked at operation. If the accessory organ is diseased, the result may be serious. It is possible that the gallbladder lying in the normal site may be found to be normal at operation while the accessory gallbladder may be the seat of trouble. If cholecystography is performed, it should be borne in mind that since a diseased gallbladder may coexist with a normal accessory gallbladder, the former may not be visualized, while the latter would reveal a normal sequence. This finding may lead to the wrong negative diagnosis.

Golob<sup>15</sup> reports a case of *diverticulum of the gallbladder*, which was diagnosed in an otherwise normal gallbladder. Pre-operative diagnosis can be made only by cholecystography. Twenty articles have been written on this subject since 1923, some under the term of pseudodiverticulosis. Six cases were detected roentgenologically, but not all were confirmed by operation. Some were diagnosed operatively and others at autopsy. That Rukstinat's three cases reported in 1936 constitute about 15 per cent of all the cases recorded in the literature attests to the rarity of the anomaly. Barsony and von Fredrick in 1928 report a case of diverticulum of the gallbladder which was cholecystographically detected and surgically confirmed. As far as they know there is no previous record of this type.

The outstanding features of cholecystitis, one of the most common inflammatory conditions met in the abdomen, are

reviewed by Womack and Bricker.<sup>16</sup> They feel that there is a definite relationship between cholecystitis and cholelithiasis, for the latter is seldom encountered in the absence of the former. Stones in the gallbladder sooner or later may be concerned with partial or complete obstruction of the cystic duct. The pathological picture in cholecystitis is unique in many respects. Gangrene is common without concomitant arterial obstruction. This is highly suggestive of a direct action of some substance which produces necrobiosis of the tissue. Acute inflammation of the organ is associated: (1) Usually with gross or microscopic evidence of preexisting inflammatory process; (2) with increased vascular permeability—edema, extravasation, and injury to tissues, and (3) nearly always with obstruction to the cystic duct. Lipids (cholesterol) may incite mild inflammation. Evidence of a deposition of bile or some of its components, in the gallbladder wall, may occasionally be seen in cases of chronic cholecystitis. From a consideration of these features, it would seem that any causative agent must have (1) the ability to produce a particular injury to tissue, (2) easy access to the gallbladder, and (3) increase of its action in the presence of obstruction of the cystic duct. The authors believe that bile may fulfill these qualifications, and studied it with the idea that it might be the causative factor in the production or instigation of cholecystitis. They found that the action of bile was dependent upon the concentration of the cholic acid derivatives. With the injection of bile into the tissues the reaction consists of gangrene, edema, ecchymosis, round cell infiltration, and fibrosis, this reaction being modified later on by secondary bacterial invasion. If complete obstruction of the cystic duct is effected, the imprisoned bile is then replaced with a

physiological solution of sodium chloride, inflammation of the gallbladder is not produced. Occlusion produces only distention with mucus unless it is associated with severe bacterial infection, when true empyema may supervene. When the cystic duct is occluded and the bile is left in the gallbladder, various degrees of inflammatory reactions are obtained. This inflammation is identical with that encountered in clinical cholecystitis. The severity and types are dependent on the content and concentration of the bile obstructed. The experiments show that this inflammation is produced by direct action of bile on tissue. Bile and its components (especially cholesterol) can be demonstrated at times in the walls of the gallbladder in cases of human cholecystitis. Bacterial infection is a variable factor in cholecystitis, and while it may be of great clinical importance, the authors believe that from the standpoint of pathogenesis, it should be considered as a complication that results when contaminated tissue is injured.

Lewis and Peterson<sup>17</sup> state that *cholesterosis of the gallbladder* may be defined as a metabolic and not an inflammatory disease in which the mucosa of the gallbladder contains deposits of cholesterol and other lipid material. In the advance stages, cholesterol calculi may be present in the lumen of the gallbladder. The characteristic pathological feature, "strawberry gallbladder," is well known. The authors report studies of 25 cases of cholesterosis of the gallbladder without stones treated by cholecystectomy. Twenty of these patients were followed postoperatively from one to ten years. Pain was a predominant symptom in this group, and 19 of the patients complained of recurrent attacks of typical biliary colic in the upper abdomen. Cholecystograms were inconclusive, only five of the cases showing nonvisualiza-

tion of the gallbladder. *Preoperative diagnostic biliary drainage revealed cholesterol crystals in the bile in 19 of the cases.* This procedure is urged as a diagnostic aid in this disease, where frequently the signs, symptoms, and roentgenologic findings may be so indefinite. Cholecystectomy gave satisfactory results. Of the 20 patients followed, 14 were relieved of all symptoms, four were relieved as long as they stayed on a low fat diet, and two patients were unimproved.

were at times asymptomatic. In all the 30 patients without stones, pain was present. One-third of them had intense typical colic and another third had pains of a rather dull, boring, and localized character in the right hypochondrium. In the last third of the cases, the localization did not directly suggest biliary tract disease. The only difference between the two groups, in regard to pain, was that the severe biliary colics were more common in the presence of stones. In cases with cholesterosis alone, symp-

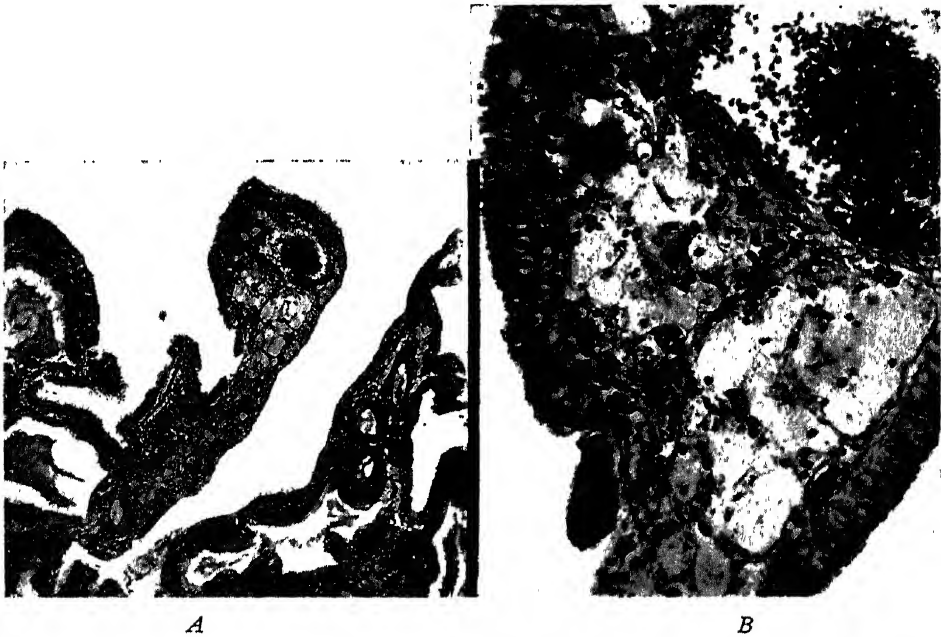


Fig. 2—A and B. Cholesterosis of the gallbladder. Note the distended, foamy cells, containing lipid in the villi of the mucous membrane. These are seen as the pale areas in the stroma. (Paraffin section: Hematoxylin-eosin—(a) Low power and (b) High power). (K. M. Lewis and C. W. Peterson: Ann. Surg.)

Arnell reports<sup>18</sup> 110 cases of cholesterosis, which were found in 7.8 per cent of a series of 1198 cholecystectomies. There was no direct relationship between the extent of the cholesterol deposit and the intensity of the symptoms. Cases with symptoms severe enough to require cholecystectomy sometimes revealed only microscopically demonstrable cholesterosis and, conversely, cases in which there was pronounced visible cholesterosis

toms persisted for years. Vomiting was one of the most common symptoms. Certain types of food were not tolerated, especially fat, meat, and vegetables, which at times caused vomiting, diarrhea, and pain. Constipation and diarrhea also occurred. Acid eructations were less common. Fever occurred in 19 cases without stone, and in nine cases associated with chills. In cases coming to operation, some showed thickened, highly

folded mucous membrane with callosities formed between the neck of the gallbladder and the cystic duct, which produced mechanical obstruction to the outflow of bile through the cystic duct and therefore produced a valvular effect. In other cases anatomical anomalies, such as kink formation of the cystic duct, a marked development of a Heister's valve, and abnormal mobility of the gallbladder made up the background of the patient's symptomatology. Complications in the form of infections in gallstones may arise in these cases. Cholesterosis may be the cause of gallstone formation. It is impossible to make a definite diagnosis except in certain polypus forms in which roentgenographic examination can settle the question. The ultimate results from operation were the same as after cholecystectomy for cholecystitis and cholelithiasis.

Gallbladder disease in 2450 consecutive autopsies, during a five-year period, at the Queens General Hospital, were reviewed by Russo and Angrist.<sup>19</sup> It was found that:

1. "Incidental" gallbladder disease with stone was found in 271 cases (11 per cent). With each decade this figure increased, reaching 25 per cent in the eighth decade. Symptoms referable to the gallbladder had been elicited in only 4 per cent of cases.

2. Seventy (25 per cent) of the 271 cases of gallbladder disease were "severe" in degree. Severe, acute pathological conditions accounted for the highest percentage of "gallbladder deaths," and perforation played a predominant rôle. Severe chronic disease was manifested principally by cases of hydrops of the gallbladder and of marked contracted chronic cholecystitis and cholelithiasis. Only one death was due to "gallbladder disease" in this group. Only five of the seventy patients who showed severe gall-

bladder disease at autopsy showed any clinical symptoms referable to the gallbladder.

3. Moderately advanced and minimal gallbladder conditions comprised 16 per cent and 59 per cent, respectively, of the entire series and accounted for no deaths.

4. Obstruction by stone was the most common lesion of the biliary ducts associated with cholecystitis in this series. The "invasion" mechanism of carcinomatous obstructive jaundice is emphasized.

5. Inflammation of the gallbladder gave rise to few instances of liver disease in this series. Biliary cirrhosis and cholangitis occurred in a relatively small number of cases.

6. Pancreatic disease resulting from acute or chronic gallbladder disease was not found frequently.

7. No appendiceal abnormality of any significance in relation to gallbladder disease was found.

8. Coronary sclerosis and general arteriosclerosis are not significantly more common among patients with gallbladder disease.

According to Christopher *et al.*,<sup>20</sup> *gangrene of the gallbladder without infection and due to infarction is uncommon.* Reference is made to 144 cases reported in the literature. It is pointed out that gangrene of the gallbladder may be due to any one of the following causes: (1) Infection; (2) edema of structures adjacent to the cystic vessel; (3) stones plus infection and pressure; (4) mechanical factors, including (a) torsion, (b) angulation of the cystic duct by distention, (c) glands or tumors, (d) embolism or thrombosis of the cystic duct (no proved case), and (e) distention spasm. There is no accurate guide to the diagnosis of gangrene of the gallbladder. There may be marked tenderness and rigidity of the upper right

quadrant, but the symptoms may be mild.

They report the case of a 59-year-old widow who suffered for 32 hours with continuous pain in the upper right quadrant of the abdomen. Several hours after the onset of the pain, nausea and vomiting occurred. A cholecystectomy was performed. The gallbladder was huge, weighing 580 Gm. and measuring 16 cm. in length. Twenty-one millimeters of cystic duct were attached. The external circumferences were as follows: Corpus, 26 cm.; fundus, 25.5 cm., and neck, 12 cm. The hepatic surface measured 12 by 8 cm. Most of the free serosal surface was smooth and light to dark red, but the corpus and neck were covered with an oblique strand of fatty adhesions attached for a distance of 11 cm. The lumen contained 200 cc. of dark green bile, 300 faceted cholesterol stones, up to 12 mm. in diameter, and myriads of smaller concretions 1 to 2 mm. in diameter. The dark red wall varied in width from 3 to 10 mm. The serosa and mucosa separated spontaneously when the gallbladder was opened. The dark green mucosa was smooth except for several submucosal linear strands. No infection or ulceration was noted. Microscopic examination showed practically no visible structures. The wall was converted into a swollen, pale pink, ghostlike structure with linear zones of polymorphonuclear leukocytes beneath the serosa. There was extensive erythrocytic extravasation throughout. There was no involvement of the cystic artery. The cause of the infarction could not be determined from the examination of the specimen.

Bagnati<sup>21</sup> points out that *total gangrene of the gallbladder* is unusual. He presents the case of a 42-year-old female who had a history of attacks of intense pain in the right hypochondrium with radiation to the shoulder, accompanied by nausea, vomiting, and severe

headache. The symptoms suggested acute appendicitis. Operation showed diffuse infarction of the wall of the gallbladder, evidently caused by a stone that had obstructed the mouth of the cystic duct. There was torsion of the gallbladder. The pathological lesions were more severe than the symptoms suggested, in fact, the symptoms had improved greatly after the patient's admission to the hospital. Operation with removal of the gallbladder was followed by uneventful recovery. The removal of the gallbladder was easy, as the gangrene had produced a line of cleavage.

It was pointed out that these cases generally occur in old people over 60 years of age. Obstruction of the cystic duct or the blood vessels seems to be the chief factor in their causation rather than infection. The cystic vein and lymphatics are frequently compressed. Another mechanism of production is embolism of the cystic artery, which cuts off the blood supply to the gallbladder. While the diagnosis is difficult, an early diagnosis is essential if perforation and peritonitis are to be prevented.

A review of the literature and a study of 150 cases of *benign neoplasms of the gallbladder* was made by Shepard *et al.*<sup>22</sup> They concluded that *the benign neoplasms of the gallbladder are polypus, adenomyoma, and fibroma*. The benign neoplasms of the gallbladder are rare, usually occurring in the middle decade of life. Polypus and adenomyoma each are found once in every hundred gallbladders removed at operation. Chronic inflammation is the constant concomitant of benign neoplasms of the gallbladder, particularly when stones are present. Cholelithiasis is frequently present in the gallbladder bearing a benign neoplasm. Chronic inflammation and trauma of gallstones probably play a rôle in the causation of the benign neoplasms. However,



congenital misplacement of tissue may be an additional factor in the causation of adenomyoma of the gallbladder.

No characteristic clinical picture is exhibited by these tumors. Symptoms and physical findings are those of concomitant chronic cholecystitis or cholelithiasis, or both. Cholecystography may be helpful in establishing a preoperative diagnosis. The incidence of malignant changes in these neoplasms is low; two malignant lesions occurred among 45 cases of polypus of the gallbladder. No malignant lesion was discovered in 103 cases of adenomyoma of the gallbladder and two cases of fibroma of the gallbladder. Intramural abscess and intramural gallstone occurred as a complication of adenomyoma of the gallbladder. Removal of the gallbladder is indicated in these cases.

**Roentgenology**—Curl<sup>23</sup> has correlated the observations reported in the literature pertaining to the influence of various factors on filling of the gallbladder with the result of cholecystography performed 512 times on 182 medical students. He concludes that fat is an essential factor in the gallbladder emptying mechanism. If the gallbladder of patients on a fat-free or a low fat diet has not emptied for days, it may be distended with thick, concentrated bile and, unable to admit more bile, will not be visualized on roentgen examination.

It is advised that for routine gallbladder examination, or when the history of cholecystitis is questionable, the patient be put on a high fat diet for several days or even weeks before the roentgen examination is made.

**Acute Cholecystitis**—In an attempt to avoid the confusion and difference of opinion regarding the treatment of acute cholecystitis, Saint<sup>24</sup> has reviewed the etiology, pathology, and symptomatology of the disease. It is pointed out that

while pathological changes, which occur in the gallbladder, result from the presence of two factors, *viz.*, acute obstruction of its outlet, and acute inflammation of its wall, the rôle played by the former is of such importance as to suggest the desirability of designating the disease "*acute obstructive cholecystitis*." The essential pathological feature is an increase in the intravisceral tension in the gallbladder, the result of this combination of acute obstruction and inflammation occurring in it. This tension may become so acute as to interfere with the blood supply and may do so to such an extent that gangrene ("tension gangrene") of the gallbladder, followed by rupture and extravasation of its contents, will take place, this catastrophe representing nature's method of relieving the increased tension within the gallbladder in the presence of an obstruction of its outlet which she is unable to remove or otherwise overcome. Should nature succeed in overcoming the obstruction, then the contents of the gallbladder can escape by the natural passages, leading to relief of the increased intravisceral tension and consequent recovery of the patient from the attack. The rational treatment aims at the prevention of gangrene, and thus of the possible complications of rupture and extravasation, by relieving the increased intravisceral tension through surgical intervention, should the disease progress to the stage when it has become apparent that nature is unlikely to succeed in her efforts to remove or overcome the obstruction. The *most important single clinical manifestation* indicating that the disease has progressed to this stage and which, therefore, indicates the necessity for immediate relief of increased intravisceral tension in the gallbladder by **surgical intervention** as the most certain means of preventing further pro-



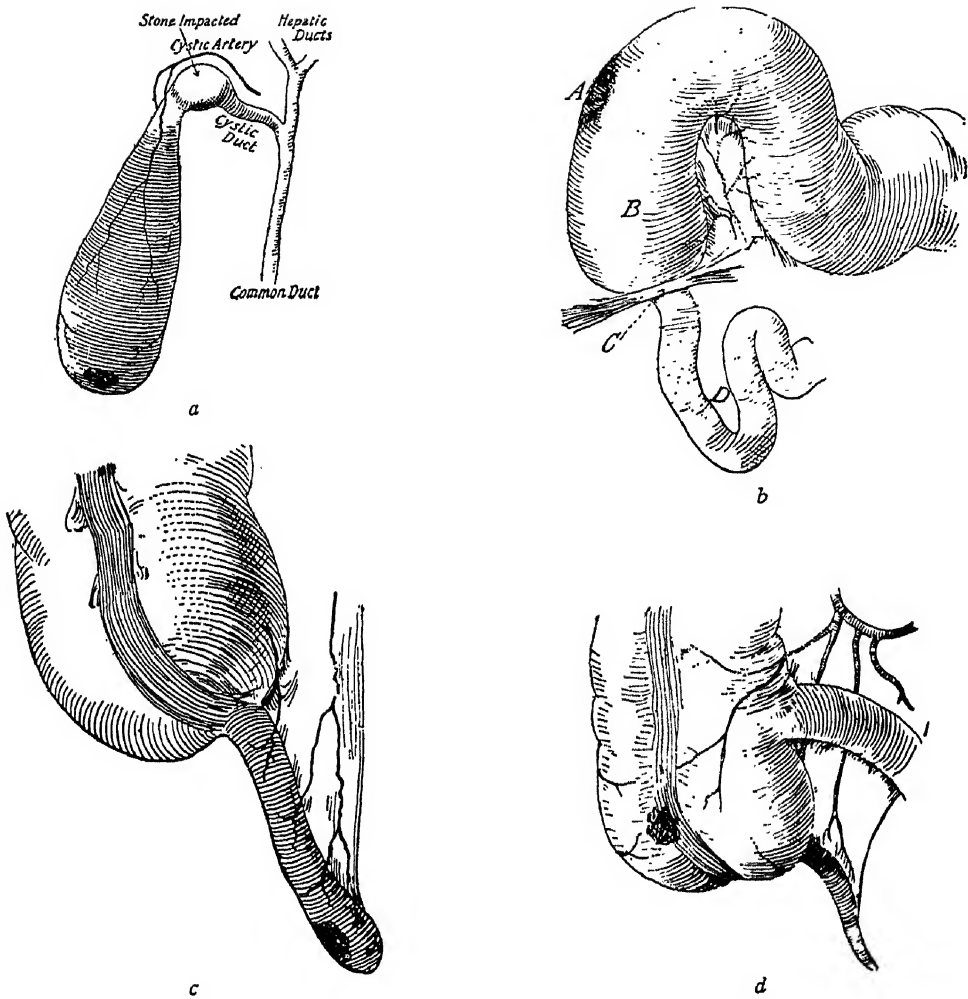


Fig. 3—Illustrations of tension gangrene occurring in various hollow muscular viscera. Note the essential presence of obstruction of the lumen as an etiological factor in each case. *a*, Diagram of gallbladder to illustrate tension gangrene. *b*, Acute intestinal obstruction of 2 days' duration: *A*, Gangrenous patch; *B*, small intestine distended; *C*, constricting band; *D*, collapsed intestine; *F*, mesenteric vessels. *c*, Diagram of appendix to illustrate tension gangrene. *d*, Diagram to illustrate tension gangrene in the cecum following obstruction due to cancer of the sigmoid. (J. H. Saint: Surg., Gynec. and Obst.)

gression of the pathological changes to the termination of "tension gangrene" is the development of a tender, palpable, gallbladder during the course of the disease.

In the 44 cases reviewed, the chief indication for operation was the finding of a tender, palpable mass in the upper right quadrant of the abdomen, the pathological significance and clinical manifestations of which have already been discussed. This was present in 28 patients when first seen and an immediate operation advised. By an immediate operation

is meant one that is conducted as soon as possible after the preoperative medication preparation, administration of sedatives, intravenous therapy, and gastric lavage are carried out. The remaining 16 cases were under observation for a length of time varying from hours to eight days. When an enlarged, palpable gallbladder was encountered, immediate operation was advised. It is pointed out that the decision of "when to operate" was not in any way related to any belief or general rule regarding the advisability of respective, "immediate," "early," or

"delayed" operation as such, but was based entirely upon the development of what are considered specific indications for operative intervention, *viz.*, the enlarged, palpable, tender gallbladder. This may be associated with spreading rigidity of the overlying muscles in the abdominal wall and an increasing pulse rate, but these are confirmatory evidence of nature's progressive pathological process. Cholecystostomy was performed in 32 cases and cholecystectomy in 12. The large number of cholecystostomies was due to early inexperience of the operator. There was only one death in the series.

The records of 140 patients suffering from acute cholecystitis were reviewed by McLanahan *et al.*<sup>25</sup> It was pointed out that the disease is one of middle or late middle life and that age played a definite rôle in the mortality. Those under 60 years of age had a mortality of 2.8 per cent, while those over 60 years of age had a mortality of 26.5 per cent. Pain, nausea, and vomiting were universal symptoms. The palpation of a mass was uncertain, since muscle spasms or other structures were confusing to the examiner. Twenty per cent of the patients were jaundiced, yet the common duct was explored only five times, which indicated a conservative policy towards this procedure. In one-half of the cases, the symptoms were of more than one week's duration before admission to the hospital. A mortality of 18 per cent occurred in those operated within the first 24 hours; however, these were the most severe cases. The patient whose symptoms persist or subside slowly should be operated on promptly to arrest any progressive pathological change. The patient whose symptoms had rapidly diminished should be given further conservative treatment and operated during the interval. Those patients, who were deemed satisfactory surgical risks, were advised

to have an operation after the acute process had subsided, as evidenced by the clinical signs and symptoms. The average duration of hospitalization for the entire group was 24 days. In the operative group, it was 31 days, but the postoperative period averaged 9½ days. In the group not operated on, the duration was approximately 12 days.

According to Zollinger and Cutler,<sup>26</sup> each patient with acute cholecystitis presents an individual surgical problem, and acute cholecystitis is such a potentially serious disease that the idea of treating the patient at home should absolutely be abandoned. Early hospitalization does not necessarily indicate that early surgery will be carried out, but it affords an excellent opportunity to institute the treatment to prepare for surgery at an ideal time. The extent and severity of the inflammatory process of the gallbladder are estimated by physical examination plus an evaluation of the patient's general condition.

Accepted conservative measures are then instituted consisting of:

1. Relieving pain with morphine.
2. Placing the patient in a semi-sitting position with heat to the abdomen.
3. Administration of fluids by the intravenous or subcutaneous routes to hydrate properly the patient.
4. Constant gastric suction, if the patient is vomiting or the abdomen is distended.
5. Routine laboratory studies are made.

Each patient should be classified clinically into one of three groups, the first group comprising the majority of patients whose signs and symptoms subside after adequate treatment, rest, fluids, and relief of pain. These patients may be prepared for operation within five or six days. The second group includes those patients whose temperature, white cell count, and physical findings remain

practically constant, with no response to the initial treatment. Thirty-six to 48 hours after the fluid balance has been adjusted, operation should be performed in this group. It should not be delayed. The third group is made up of a small number of patients whose signs and symptoms show rapid progress. These patients are acutely ill, and usually require simple drainage of the gallbladder as soon as possible.

These clinical groups and their response to standard conservative measures provide a clue to the selection of the proper time for surgery—either early or delayed. Sufficient time must be allowed to correct dehydration before operation. The incidence of complications associated with acute cholecystitis is high, being 24 per cent. The majority of these are associated with the pulmonary system. Wound infections are second in frequency. Although removal of the gallbladder is more desirable, simple drainage seems to be the operation of choice in selected cases.

In discussing this paper, Behrend points out that he does not subscribe to the idea that acute cholecystitis is an emergency operation. He insists upon hospitalization of patients, treats them medically until the acute attack subsides. He points out that if rupture should occur while in the hospital, the patient should be subjected to immediate surgery. He has not performed a cholecystostomy in the last ten years for acute cholecystitis.

In reply, Dr. Cutler states that his mortality has definitely improved since cholecystostomy was performed on the critically ill and elderly patients with burst gallbladder or seriously incapacitated, poor risk individuals.

Ramey and Scott<sup>27</sup> report 110 cases of acute cholecystitis; 69 were operated upon and 41 were treated medically.

The average age of the patients in the entire group was 52 years; for those operated on it was 51 years, and for those not operated on it was 54 years. Many in the latter group were in the seventh and eighth decades and for this reason alone, operation was not advised. All cases were placed on medical management when admitted to the hospital. Those who were deemed satisfactory surgical risks were advised to have an operation after the acute process had subsided.

Of the 69 cases who were subjected to surgery 54 (78 per cent) had a cholecystectomy and 14 (21 per cent) had a cholecystostomy. Three patients had drainage of the common duct in addition. In one a malignant ulcer of the stomach was noted and treated. The subacutely inflamed gallbladder was not disturbed.

Of the 110 patients, eight died; four of these had cholecystostomies, and the deaths were due to cerebral embolism, bronchial pneumonia, myocardial failure, and suppurative cholelithiasis. There were four deaths in the unoperated group. In one, perforation of the gallbladder was responsible, in two uremia was the cause of death, and in the last it was myocardial failure. Empyema of the gallbladder was encountered in 21 of the 69 operative cases. In 14, gallstones were present. The average white count was approximately 12,000, with 81 per cent neutrophils. The average temperature elevation was 100.4° F. Ten of the patients had chills, with a present episode of acute disease. The gallbladder was removed in nine and drained in 12. There were three deaths in this group alone. The authors believe from their observations that the policy of waiting from seven to ten days for diagnosis or preparation of the patient and for subsidence of the symptoms is justifiable.

TABLE I  
RELATIONSHIP OF DURATION OF DISEASE TO INCIDENCE OF GANGRENE AND PERFORATION\*

Time of Operation	Acute Cholecystitis, Cases	Gangrene of Gallbladder, Microscopic Evidence		Perforation of Gallbladder, Surgical Evidence	
		No.	Per Cent	No.	Per Cent
Immediate.....	32	9	28.1	2	6.2
Early.....	27	8	29.6	3	11.1
Delayed.....	68	28	41.1	17	25.0
Total.....	127	45	35.4	22	17.3

\* G. T. Root and J. T. Priestley: Am. J. Surg.

A complete analysis of the 110 cases managed conservatively with a total mortality of 7.23 per cent is presented.

Root and Priestley<sup>28</sup> point out the difficulty in selecting cases for statistical purposes in the evaluation of acute cholecystitis. As an example they state that between July, 1936, and April, 1942, there were found to be recorded 248 cases in which a diagnosis of acute cholecystitis had been made by pathology (89 per cent of which were also believed by the surgeon to be acute cholecystitis), but none of these had been considered to be acute cholecystitis preoperatively. The mortality rate in this group was 2.8 per cent. By way of contrast, in a series of 127 patients who had acute cholecystitis treated surgically, and who had a preoperative diagnosis and a pathological diagnosis of acute cholecystitis, there was a mortality rate of 6.2 per cent. This shows the confusion which may arise unless uniform classification of acute cholecystitis is adopted by all authors. The relationship of the duration of the disease to the incidence of gangrene and perforation is well illustrated in Table I. It was observed in this series that the incidence of gangrene and perforation increased as the duration of the disease increased. It was also noted that the incidence of associated hepatitis and pan-

creatitis increased as the disease progressed. The feasibility of performance of cholecystectomy, in contrast to the feasibility of performance of cholecystostomy, was greater within the first 72 hours after the onset of acute cholecystitis than at any subsequent time prior to the subsidence of the acute process. Various complicating features associated with the surgical treatment of cholecystitis are more likely to occur when the operation is performed for acute cholecystitis than when the operation is performed for chronic cholecystitis.

Brooks *et al.*<sup>29</sup> review 110 cases of acute cholecystitis; the average period of preoperative preparation was found to be 37 hours. In this series the average duration of the acute illness before hospitalization was found to be 5.2 days. The postoperative complications of acute cholecystitis are: Pneumonia, atelectasis, and cardiovascular disease. Mortality rate in this series was 3.6 per cent. The causes of the four deaths were pneumonia, coronary thrombosis, pulmonary embolus, and generalized peritonitis with atelectasis.

Lawrence and Clute<sup>30</sup> point out the necessity of differentiating clinically between acute cholecystitis and certain other conditions of the upper abdomen that may be treated without operation.

This is necessary because the principle of early operation has been accepted as the safest method of managing acute cholecystitis. Pathological changes and sequelae, which followed acute obstruction of the cystic duct, are discussed. A typical clinical picture of acute cholecystitis is discussed. *The diseases of the liver which may simulate the clinical picture of acute cholecystitis* are postulated as follows: Necrosis in a tumor nodule, growing more rapidly than its blood supply, which causes a considerable reaction on the peritoneal surface; stretching of Glisson's capsule, by an underlying hemangioma, abscess, or echinococcus cyst of the liver, and a more diffuse hepatic inflammation causing pain through both the mechanisms mentioned plus possible affection of the visceral sensorium, for example, a fulminating acute hepatitis or yellow atrophy. Fever, leukocytosis, systemic disability, or reflex gastrointestinal symptoms may be as commonly associated with certain of these conditions as with acute cholecystitis.

The clinical picture of acute cholecystitis may be simulated by primary or metastatic cancer of the liver, particularly when a secondary hemorrhage or necrosis has occurred. A history of previous malignancy should make one suspicious.

A case of a 56-year-old woman complaining of pain in the upper right quadrant of five days' duration was presented. Pain was associated with mild chills and fever. There has been some weight loss—34 pounds in about three months. On examination, a tense, rounded, tender mass, the size of a small cyst, was felt in the gallbladder region. The liver edge was palpable 5 cm. below the right costal margin, rounded and tender. Adenocarcinoma of the anterior rectal wall was also found. At laparotomy, the mass

proved to be a hard tumor nodule imbedded in the liver.

Another case of acute hepatitis was presented in order to show the difficulty in differentiating this condition from acute surgical conditions of the upper abdomen. A history of exposure to a hepatotoxin should make the surgeon suspicious. The case presented was a 36-year-old Negro complaining of severe retching, vomiting, malaise of 3½ days' duration. He dated his illness to the inhalation of fumes from a broken fire extinguisher bulb containing carbon tetrachloride. In addition, there was a history of taking *sulfanilamide* and also chronic alcoholism. The upper two-thirds of the abdomen, on the right side particularly, was nearly boardlike and exquisitely tender. The white cell count was 31,000. The urine contained traces of bile. X-rays showed the liver to be somewhat enlarged, but no free gas. Despite an atypical history, it was believed that the signs were those of acute upper abdominal peritonitis, possibly from a perforated gallbladder or a peptic ulcer, and an immediate operation was performed. On opening the abdomen, an acute hepatitis with free bile-stained fluid and toxic regional lymphadenitis was found. Patient died 4½ days later. Autopsy revealed central necrosis of the liver, probably due to carbon tetrachloride.

**Symptomatology as Related to Treatment**—Cutler<sup>31</sup> points out that gallstones are relatively frequent and their incidence increases with longevity. Women are affected three times as often as men. The finding of stones without symptoms is no reason for surgery.

Two-thirds of the patients with chronic cholecystitis give a history of upper right quadrant pain, referred to the back, while not more than one-third complained of epigastric distress, in contrast to patients with acute cholecystitis or common duct

stone, whose epigastric pain is possibly due to pancreatic involvement. About 10 per cent have left upper quadrant or left infrascapular pain, and often have been diagnosed as having angina pectoris. Vomiting is not a common symptom unless the calculus is located within one of the major hepatic ducts. Many patients give a history of chronic indigestion unrelated to their dietary regime or physical activity. Typical attacks of colic and jaundice obviate the necessity of an x-ray examination. Physical examination is often inconclusive between attacks, except for probable evidence of obesity. The serum diastase and icterus index may be elevated. One of the most frequent and serious mistakes a surgeon makes in the treatment of chronic cholecystitis is failure to remove extra hepatic bile duct stones. The incidence of choledochostomy in patients with cholelithiasis should be between 40 and 50 per cent of all operations for stones and adds little to the risk.

The diagnosis of stone in the common duct is made in the presence of colic, vomiting, chills and fever, jaundice, and a past history consistent with the diagnosis of cholelithiasis. It occurs nine times in women to once in men. In the presence of jaundice, Crovasea's law should be invoked. If the blood diastase is elevated, surgery should be delayed until the level falls to normal, which is usually in three to four days. When the prothrombin time is extended, *vitamin K* should be given until a normal level is found, as well as during the first week of convalescence. A *high intake of carbohydrate* must be insured, *as well as of protein* (which can be given intravenously as plasma or serum).

Acute cholecystitis is manifested by pain beneath the right costal margin or epigastrium, which is constant and

steady in nature. Tenderness and spasm are usually present, but a palpable mass can be felt in only one-third of the cases. Fever and leukocytosis are present. In the treatment of these patients, immediate hospitalization is advised. About one-half will respond to conservative measures, consisting of administration of *fluids intravenously, sedatives, and heat to the abdomen*. Frequent evaluation of signs and symptoms and laboratory data must be made and the optimum time for operation, early or delayed, should be determined by the patient's response, each case being an individual surgical problem. *Cholecystostomy* is the operation of choice in the fulminating cases, and this group should have subsequent *cholecystectomy*.

The chief technical consideration is adequate exposure. Visualization of the common duct before applying clamps to the cystic duct is a vital safeguard. All gallbladders which impair vision should be emptied with a trocar. Blind clamping above the cystic duct is dangerous as many anomalies of the cystic artery are to be found. The defect in the liver bed should be closed and a rubber covered drain inserted. If *choledochostomy* is to be performed, the common duct is open between silk sutures, probed, scooped, irrigated with saline solution. The smallest possible catheter is sutured upward into the common duct and is pulled out of the wound in five or six days. Drainage of the biliary tract is merely a safety valve and not more than 300 cc. of bile should be collected in any given day. Each case should be followed adequately in order to appraise the operative procedure fairly.

According to Glenn,<sup>32</sup> there are several conditions encountered in surgery of the biliary tract that may better be treated if a policy of early operation is

followed. In the successful employment of such a policy, preoperative preparation must always be adequate and the prompt indications to surgical therapy recognized. Each patient is an individual and requires attention particular to his needs. If these facts are kept in mind, early surgery and acute cholecystitis, intestinal obstruction due to gallstones and associated biliary surgery, common duct obstruction, trauma to the liver, torsion of the gallbladder, biliary peritonitis, and cysts of the common duct may further

a complication in a long-standing biliary tract disease.

3. A multiparous woman of 50 was known to have biliary tract disease for 20 years. She was admitted with acute cholecystitis and obstruction of the common duct. A cholecystostomy was done due to an overwhelming blood stream infection. Death occurred 26 days later. Autopsy showed a thrombosis of the right hepatic artery.

4. This case is an example of a patient with long-standing biliary tract disease, who developed an acute obstruction due to an impacted stone in the ileum.

5. A patient, who reached adult life before a cyst of the common duct became sufficiently

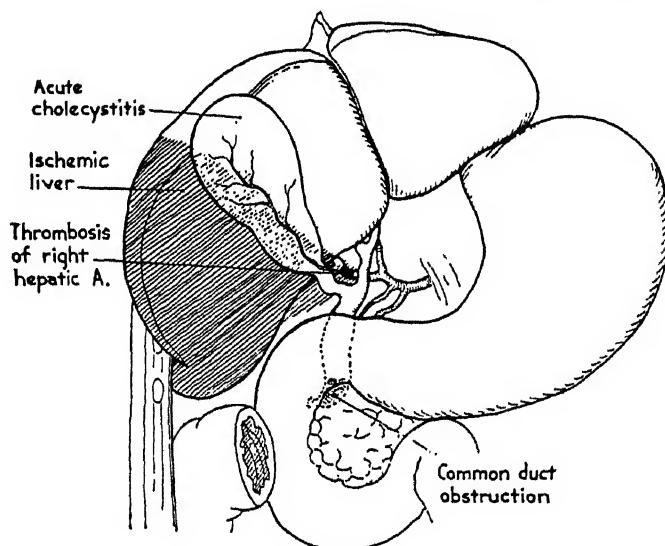


Fig. 4—Schematic drawing of acute cholecystitis. Common duct obstruction believed to have resulted in thrombosis of the right hepatic artery and accompanying ischemia of the liver. (F. Glenn: Am. J. Surgery.)

reduce our present morbidity and mortality figures. Case reports of illustrative cases are recorded:

1. An instance of a patient with preperforation of the gallbladder who was operated upon early with recovery.

2. A 66-year-old woman, suffering from poorly controlled hyperthyroidism, developed an acute cholecystitis with a known history of at least eight years of biliary tract disease. The acutely inflamed gallbladder perforated through a congenital sacculation, leading to a terminal peritonitis. Had the patient been operated upon before perforation occurred, the outcome might have been averted. This is an example of an acute cholecystitis which was not treated surgically until almost ten days after the onset. The attack of acute cholecystitis was

large to produce symptoms, was given treatment consisting of decompression by drainage of the cyst and later anastomosing the cyst to the duodenum. The result was satisfactory.

6. A 75-year-old patient, presenting the symptoms of an acute condition of the abdomen, which necessitated exploration. The bile peritonitis which was found was the result of spontaneous rupture of the biliary tract. Death occurred four days postoperatively. The pathologists found at autopsy a rupture of the cystic duct. This was the source of a large amount of bile found free in the peritoneal cavity. In addition, there was pancreatic fat necrosis and acute cholecystitis.

Glenn advocates a policy of early operation in jaundice in order to cut down on the instance of liver damage. Simple



drainage by *cholecystostomy* is preferable to letting these patients continue on with their obstructive symptoms.

**Surgical Technic**—The importance of adequate surgical exposure of the gallbladder and common bile ducts was em-

to the left so that any bands between the duodenum and the gallbladder are put on the stretch and severed. The hepatic flexure, which is often fixed by bands to the undersurface of the liver, is freed so that the flexure can be com-

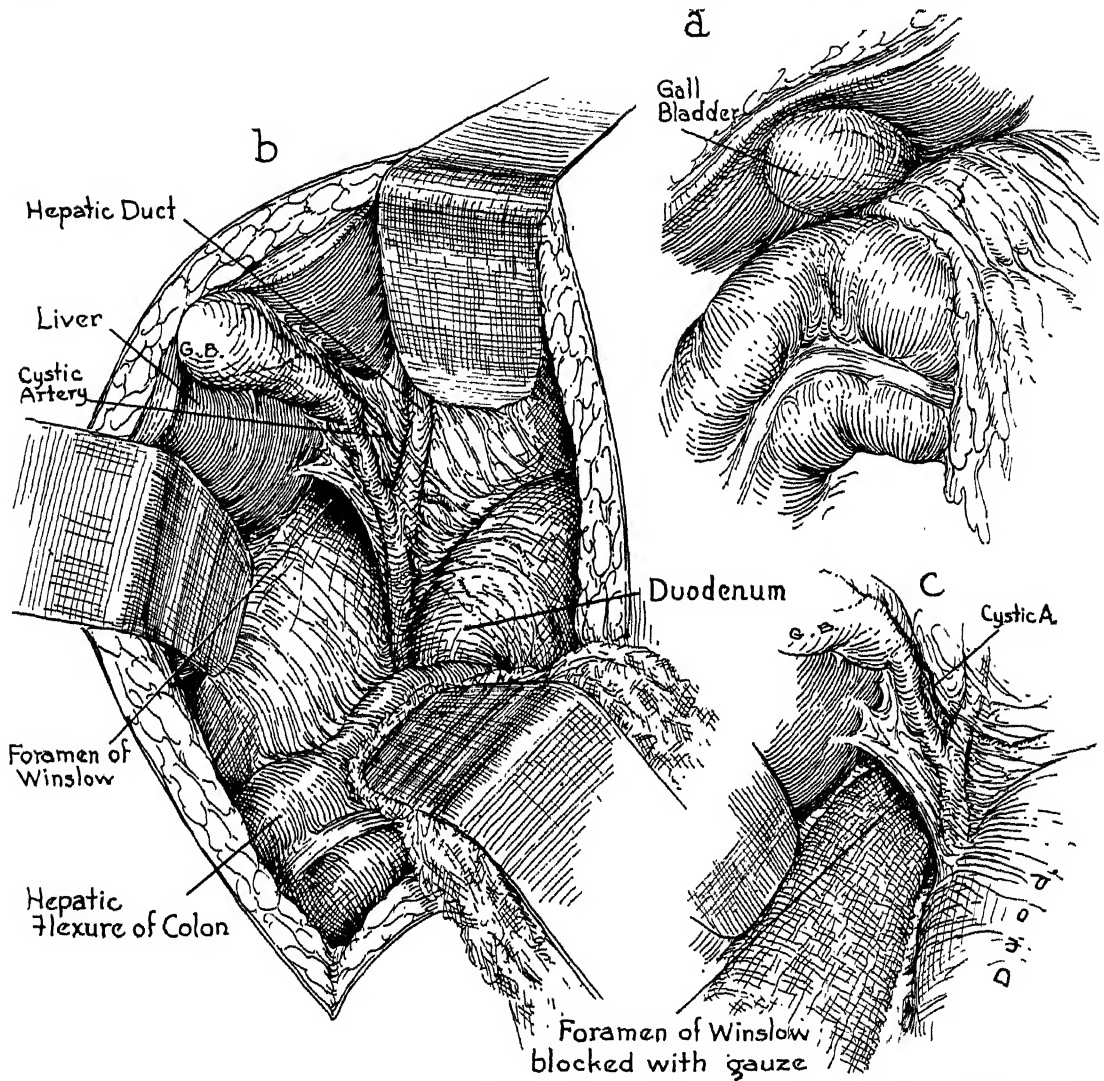


Fig. 5—*a*, The anatomical relations of the gallbladder and hepatic flexure when the abdomen is first opened. *b*, The hepatic flexure and duodenum mobilized to the left and held in position with retractors upon gauze pads. The clamp on the gallbladder is not shown, but by traction and mobilization of the duodenum and hepatic flexure to the left this exposure of the duct and foramen of Winslow is obtained. Note also the visualization of the cystic artery with the peritoneum over the duct opening. *c*, The foramen of Winslow blocked with gauze. (F. H. Lahey: Surg., Gynec. and Obst.)

phasized by Lahey.<sup>33</sup> He emphasizes spinal anesthesia and an incision of adequate length. The gallbladder is then exposed and grasped with a right angle clamp. The gallbladder is pulled upward and outward, and the duodenum is pulled

pletely dislocated to the left. A long folded wet pad is then placed over the outer edge of the duodenum up to the pylorus and, with a Deaver type of retractor placed over it, retraction is made to the left. The hepatic flexure and

ascending colon are pushed over to the left and another gauze pad is placed over their external edges. A second Deaver type of retractor is placed over this area and the flexure and ascending colon are pulled to the left. This procedure, the retractor pulling the wound edges apart, completely exposes the pouch of Morison. The common and hepatic ducts are put on the stretch as these two structures—the duodenum and the hepatic flexures with the retrocolic duodenum behind it—are pulled to the left so that the ducts are made completely visible. If another clamp is now placed upon the ampulla of the gallbladder, and the gallbladder further elevated, traction on the cystic duct will not only demonstrate the duct and its entrance into the common duct plainly, but will also open the foramen of Winslow, which should be separately packed. This packing of the foramen of Winslow prevents contamination from bile or blood which may accumulate at the deepest point of the operative field. With this exposure, flaps of peritoneum can be safely cut from the gallbladder with which to cover its bed after removal. The course and position of the hepatic artery, and the course and relation of the cystic artery to the cystic duct can readily be demonstrated and visualized. Accurate dissection of the cystic duct, down to the point of entrance to the common duct, can be accomplished. Not infrequently the discharge of bile from the torn small accessory ducts occurring at this point can be demonstrated, the open end of the accessory duct picked up and tied, and the postoperative escape of bile into the wound from the open end of an accessory duct prevented.

The author felt that when there was an escape of bile after cholecystectomy it is in most cases from tears not discovered and therefore not ligated in the accessory bile ducts. This may prevent

biliary peritonitis. With this exposure the cystic artery can be found first, carefully dissected, cut and clamped. Then the dissection between the cystic, common, and hepatic ducts can be very accurately made. It was felt that this method of exposure was the important factor in reducing the mortality both from cholecystectomy and exploration of the common bile duct. He does not feel that traction upon the duodenum and the hepatic flexure, on top of gauze, in any way increases the postoperative distention or complicates the postoperative recovery.

In cases in which the general condition makes the risk of cholecystectomy too great and cases in which removal of the gallbladder is hazardous because of these local lesions, Carpenter and Vale<sup>34</sup> advocate *chemical cauterization of the mucosa*. During the past five years the authors have had occasion to perform this operation in 47 cases. In general they were pleased with the smooth convalescence of the patients in spite of the acute condition found at operation. No case developed a persistent fistula, and in six cases the operation was combined with exploration of the common duct. They felt that there was a lower rate of recurrence of symptoms than following cholecystostomy. The technic used was to open the gallbladder, aspirate the bile, remove any stones present, and treat the mucosa of the gallbladder with four to six applications of 95 per cent solution of phenol, each of which was followed by the application of 95 per cent solution of alcohol, and drying with a sponge. No attempt was made to block the cystic duct. A soft rubber tube was inserted down to the ampulla, and the redundant gallbladder folded and sutured about this tube, which emerges through the fundus and is allowed to drain from eight to ten days. No other drainage in the abdomi-

nal cavity was done. This technic does not alter any procedure which may be necessary on the common duct or any other intra-abdominal viscus. The term chemical cholecystectomy is a misnomer, because the gallbladder mucosa is not completely destroyed and the deep glands apparently are a source of new epithelium.

*temporary occlusion of the portal vein and hepatic artery.*

In the first patient during a fifth operation for biliary obstruction, the portal vein was accidentally incised within the liver as the hepatic orifice of a biliary fistula was being enlarged. For three days hemorrhage was partially controlled

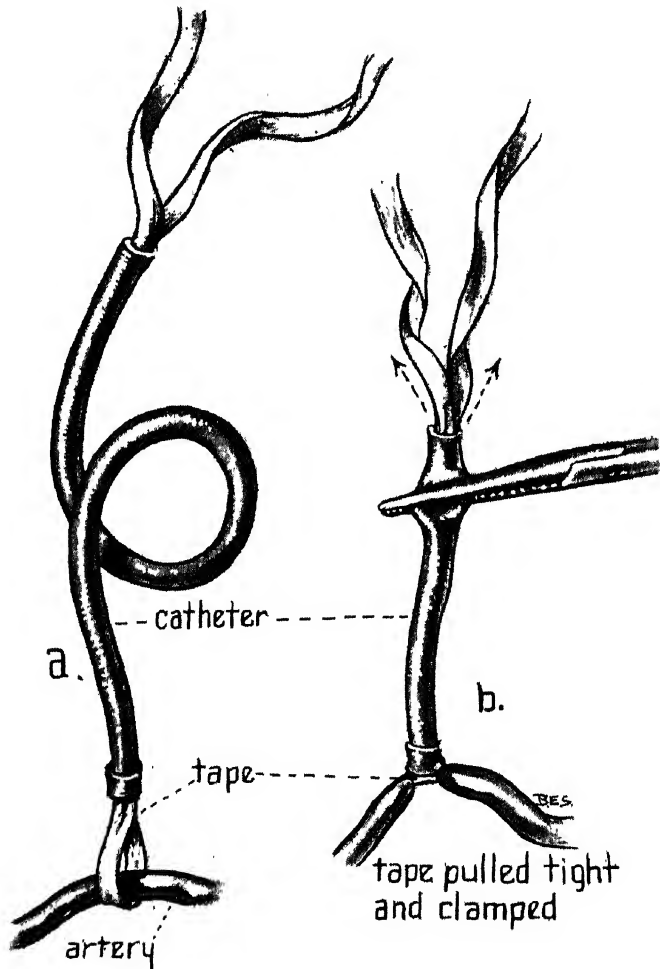


Fig. 6—Simple device used for the temporary occlusion of large blood vessels. The rubber tube may be of sufficient length to be clamped outside the wound. (W. W. Babcock: Ann. Surg.)

Résumés of five cases of suture or surgical occlusion of wounds of the portal vein recorded in the literature are presented, and Babcock<sup>35</sup> described two of his experiences with surgery involving the portal vein. His cases illustrate the feasibility and occasional usefulness of

by hemostatic forceps and then, under provisional clamping of the portal vein and hepatic artery, the opening in the portal vein was closed successfully with sutures. It was estimated that the vessels were occluded for 18 minutes. There was a marked fall in blood pressure,

which probably was due in part to loss of an estimated 500 cc. of blood. The patient had a rapid and uninterrupted operative recovery. Two months later the wound was healed except for small, freely draining biliary fistula. Operation was undertaken to anastomose the fistula to the duodenum. The subsequent course was one of general improvement, but with occasional attacks of pain and jaundice.

The second patient had a malignant cholangioma of the left lobe of the liver. The hepatic artery and portal vein were occluded by means of a tape passing through a rubber tubing, and the left lobe of the liver was removed. The operation required more than two hours of occlusion of the vessels. Bleeding from the divided liver surface was arrested by transfixing sutures of catgut, by individual ligation, and gauze packing. At the end of the operation, the patient was considered in fair condition. The patient survived for five days during which time a total of 2030 cc. of serum and blood were aspirated from the abdominal cavity.

*The period of safe occlusion of the portal circulation in man remains to be determined.* It appears that with growth of a tumor, as in the second case, collateral circulation develops, which permits a rather long period of occlusion. When the portal circulation is occluded the surgeon should be prepared to release the constriction quickly if engorgement of the mesentery vessels results in fall of blood pressure.

A series of 373 consecutive **cholecystectomies without choledochotomy**, in which no drainage of the peritoneal cavity was employed in 306 cases and some form of drainage was introduced in 67 cases, was reported by Bettman and Lichtenstein.<sup>36</sup> There were five deaths in the entire series or 1.3 per

cent; none of these were related to the absence of drainage. The cause of death was postoperative pneumonia in one case, in two the result of evisceration, in one pulmonary embolism on the ninth day, and in the other a possible coronary occlusion. The deaths all occurred in the nondrained cases. Serious postoperative complications occurred six times in 306 undrained cases, *viz.*, four eviscerations and two postoperative pneumonias; one of the pneumonias eviscerated, and later developed a subphrenic abscess. None of these patients died. Serious nonfatal complications developed six times in the drainage cases for 8.9 per cent as compared to 1.9 per cent in the undrained cases. The complications were: Hemorrhage, one; three cases of subphrenic abscess; one pneumonia, with pleural effusion, and one massive collapse of the lung. All these patients recovered. The proportionately higher ratio of postoperative complications in the drained cases may be explained on the basis of drainage being employed in the more serious cases and those in which postoperative complications may be anticipated. In no case in the series did so-called bile peritonitis develop. However, during that time three cases of bile peritonitis were noted in consultation following simple cholecystectomy. In each of these cases, drainage had been employed. Despite the drainage, bile may accumulate in large quantities in the peritoneal cavity and produce symptoms. The authors were unable to explain what happens to the bile that is seen for a few days in cases where drains were employed. They feel that leaving the drain out may prevent this biliary drainage which is frequently seen.

As a result of these studies, *the authors feel that it is perfectly safe, and probably desirable, to close the abdomen without drainage following cholecystec-*

tomy, in which choledochotomy has not been performed. This discussion does not include acute cholecystitis where the authors feel that drainage may or may not be employed depending upon local conditions. It was felt that the clean, even convalescence in this group of patients may be explained on the basis of withholding drainage.

Gonzalez Bueno,<sup>37</sup> after a series of more than 2000 operations on the digestive tract, concluded that the postoperative care should be simplified. He reviewed a series of 74 consecutive laparotomies in which the stomach, the biliary tract, the liver, and the intestines were operated upon. Local anesthesia was used. *After the operation, the patients put on their own clothes and left the operating room on foot.* For two days they were kept in special rooms where they sat in easy chairs. They were urged to move their extremities frequently and to take deep breaths. Some even went for a walk. After two days they returned to their wards, where they were comparatively active. No untoward effects were observed. There were no pulmonary, circulatory, or renal complications. There were no hematomas or dehiscences. The surgical technic should be accurate, delicate, and rapid.

**Statistical Study**—A study of 337 cases of gallbladder disease was presented by Russo.<sup>38</sup> Pathological findings are presented as a basis for understanding the 35 deaths which occurred. An appraisal of the end results in the 302 living patients was also made. It is interesting to note that the best clinical results were obtained in the groups which at the same time showed the highest mortality, *viz.*, cases presenting an acute gallbladder condition without jaundice, in which the mortality was 21.4 per cent, and the cases presenting jaundice at operation, which suffered a mortality of

27.5 per cent. It is pointed out that the clinical results classified as very poor were among the cases in which the morphological and functional changes were classed as minimal. Nine of the 35 surgical deaths were attributed at least in part to a cardiac factor. Acute inflammatory changes were present in 16 of the 35 patients and an acute pathological condition was the main factor in the death of seven of the 35 patients. A perforation of the gallbladder was relatively infrequent, occurring in eight patients, only two of whom lived. Chronic gallbladder disease was a significant factor mainly because it gave rise to impaction of stones in the biliary ducts, to the fibrotic occlusion of the ducts, and to the development of marked liver damage with biliary cirrhosis. There were 10 deaths traceable to the accidental factor, postoperative hemorrhage having been responsible for five. Common duct injury was noted in two cases, and ligation of the right hepatic artery with marked necrosis of the right hepatic lobe occurred once, as did a tear in the duodenum. Among 40 jaundiced patients there were 11 deaths. Four of these were attributable to major accidents, and two were clearly due to cardiac failure. In the follow-up study it was determined that the poorer clinical results were obtained among patients who presented a less definite or minimal disorder. In the group studied, the male patients were usually older. They presented a severe acute type of disease more often, and among them the mortality rates were high.

Castleton<sup>39</sup> reports a series of surgical cases involving the biliary tract which were operated upon by 77 different surgeons. Total number of cases was 411. A comparison of the type of operation and the mortality as compared with other series reported in the literature is best seen by Table II. The mortality rate for

TABLE II

	Ectomy		Ostomy		C. D. Explor.		All Cases	
	No.	Mortality, Per Cent	No.	Mortality, Per Cent	No.	Mortality, Per Cent	No.	Mortality, Per Cent
Cheever.....	260	0.8	...	.....	166	4.8	452	4.1
Bachhuber.....	566	6.4	67	11.9	64	20.3	630	8.41 (Excludes secondary ops. and tumors)
Grey Turner...	790	3.55	Ectomy and Ostomy		220	13.18	1040	5.86
Haggard and Kirtley.....	749	6.6	Ectomy and Ostomy		86	10.4	841	7.3
Boyd.....	412	11.2	39	30	43	11.5	1018	10.5
Whipple.....	527	1.1	29	6.1	162	26.5	840	
Allen.....	1183	2.45	130	12.3	775	4.25	2088	3.73 (Excludes cancer and bile duct injury)
Heyd.....	2438	3.61	43	30.24	296	16.5	3986	7.7
Heyd.....	428	7.47	45	28.8	98	14.2		
Lahey.....	...	.....	...	.....	...	.....	2346	3.8
Glenn.....	...	.....	...	.....	112	12.5		
Walters.....	...	.....	...	.....	...	.....	930	1.8
Walters.....	1018	1.8	65	10.8	364	3.0		
Goldman.....	343	1.7	6	0	86	5.8	...	(No plastic cases)
This series.....	301	3.98	61	14.7	40	15.0	411	7.05

\* K. B. Castleton: Am. J. Surg.

the group was rather high, being 7.2 per cent for patients or 7.05 per cent for operation. The common duct was explored in only 9.07 per cent of the cases (excluding three cases of plastic operations of the duct). This is low according to present indications; however, it carried a mortality rate of 15 per cent. The author did not feel that exploration of the common bile duct was to be done by the average surgeon without realizing the difference in mortality.

**Complications — Perforation** — According to Stout and Hibbard,<sup>40</sup> perforation of the gallbladder should be classified under five general types: (1) Perforation with communication with another viscus; (2) perforation with formation of a pericholecystic abscess; (3) acute free perforation; (4) perforation

into the liver; (5) external perforation. Etiology is essentially that of cholecystitis and cholelithiasis plus some other factor or factors which are not established. Age may be a factor. In the six cases presented the constant symptom was pain in the gallbladder region, usually very severe, but not diagnostic of perforation. There was usually nausea and vomiting, and sometimes jaundice. The onset was usually acute although a definite history of indigestion, dyspepsia, and gallbladder colic was listed in all cases. Tenderness over the gallbladder was the only constant finding. Rigidity was present when the perforation was free, and in the case in which a pericholecystic abscess had formed, there was a palpable mass as well as rigidity. Rigidity was not present when perforation had occurred

into the liver. The temperature was below normal at first in the acute free perforated cases, but later was elevated, and was elevated in all other types of cases. The laboratory findings were of little value. The x-ray is of negative value only in ruling out intestinal obstruction and perforation of the stomach.

x-ray studies. Additional evidence may be secured by the demonstration of a cholecystenteric fistula. Enterotomy is the operation of choice with the use of decompression from above.

Three cases of gallstone ileus are presented by Hand and Gilmore.<sup>42</sup> The three cases occurred in a small hospital



Fig. 7—Lipiodol injection of sinus tract. (L. M. Rankin, S. A. Eger, and H. S. Bourland: Ann. Surg.)

**Gallstone Ileus**—Hinchey<sup>41</sup> reviews 13 cases of gallstone ileus. This type of obstruction is a complication of chronic disease of the biliary tract. Earlier operation on these structures will lessen the occurrence of gallstone ileus. Diagnosis is rarely made prior to operation or autopsy. In an elderly patient, usually a woman, with a history of gallbladder disease, the occurrence of a nonfulminating, recurring, obstructive syndrome, with perhaps a shifting focus of symptoms, suggests obstruction caused by a gallstone. This may be corroborated by

within a period of two years. Preoperative diagnosis was suggested in one case, and was made with certainty by the aid of x-ray in the others. One patient had a recurrence of gallstone ileus within the first week of convalescence which was likewise diagnosed and treated successfully. The recurrence of the obstruction in this case may have been avoided if a thorough search of the entire small bowel had been made at the first operation. However, the presence of the second gallstone was unsuspected because at first laparotomy the intestinal loop, proximal



to the stone, was collapsed. The site of obstruction was in the jejunum in two cases, including the one where the stone was overlooked, and in the other case, the stone was located in the transverse colon.

**External Biliary Fistula**—The occurrence of spontaneous internal biliary fistula has been frequently reported in the literature. An extremely rare case of spontaneous external biliary fistula was reported by Rankin *et al.*<sup>43</sup>

A 78-year-old male presented the following history: Ten years previously he had had a typical gallstone colic with severe pain, which recurred at irregular intervals during the following years, lasting two to three days each time. The next attack occurred in 1938 and was no different from the former attacks. In February, 1940, a painless lump appeared just below the right costal margin, one inch lateral to the mammary line, which gradually increased in size and became markedly superficial, and in August, 1940, spontaneously ruptured through the underlying skin. The discharge contained pus and several small gallstones, but no bile.

Upon examination, the man was found to be well preserved for his age. When dressing was removed a mucopurulent discharge with six gallstones were found lying on the skin about the fistulous opening. There was no evidence of acute inflammation. Several small stones were removed from the fistulous tract. Lipiodal was injected into the fistulous tract. The roentgenogram showed that the lipoidal collects in a cavity that has a size, shape, and position consistent with the gallbladder. It is not completely filled and there are irregular filling defects in the upper end of the gallbladder due to nonopaque calculi. The cystic and common ducts are filled with radiopaque oil and a small amount had passed into the duodenum. Two days later an oral cholecystogram showed the gallbladder did not visualize. He was followed regularly in the clinic until May of 1941, during which time the fistulous tract remained open, occasionally discharging a stone, but no bile. The patient was then lost track of without surgical intervention, due to age.

**Follow-Up Studies** — Verbruycke<sup>44</sup> points out the possibility of encountering at operation a soft bluish gallbladder, in cases where gallbladder disease has been

diagnosed by all possible means. He collected a series of 32 cases of comparatively normal appearing gallbladders which he removed. In some, cholecystic adhesions were present; in others there was a hepatitis, but in none was there evident gross pathology in the gallbladder itself. The end-results were traced for years in these cases. Satisfactory results were obtained in 87.5 per cent of the cases without operative mortality. In his opinion, it is perfectly justifiable to remove the gallbladder, although its gross appearance may be normal, if no other cause for the patient's complaints can be found at operation.

He quotes Catell, who believes that a gallbladder should be removed when there is a history suggesting cholecystic disease, when the cholecystograms are suspicious looking or show pathology, and when other gastrointestinal disease is ruled out.

In a group of more than 2500 patients operated upon for cholecystic disease, Foss<sup>45</sup> found that 149 (5.6 per cent) returned for further surgical care. Many patients were operated upon because of an unnecessary previous operation, usually a cholecystectomy for the so-called "noncalculous cholecystitis." This condition is rarely a sufficient indication for surgery. Of a group of 100 patients who had previous cholecystostomies, 58 per cent had gallstones, either overlooked at the first procedure or subsequently removed. **Choledochostomy** was necessary in 34 per cent of the entire group, largely because of stones found in the common duct which had been overlooked previously. Six patients had a common duct stricture resulting in most instances from traumatism of the duct at the time of the previous cholecystectomy. Fifteen patients were readmitted because of chronic postoperative biliary fistulas. All were cured by excision of

the sinus or of the gallbladder, or by various plastic operations on the common duct. Three cases of carcinoma of the biliary tract were discovered. The mortality of the entire group was 8 per cent. While patients with extensive cholelithiasis may be entirely symptomless, the disease is nevertheless continuous and progressive, involving the gallbladder, ducts, liver, and pancreas. Acute empyema or common duct obstructions with secondary pancreatic involvement may occur at any time. Once the diagnosis of gallstones is made, operation should be done; this almost always means **cholecystectomy**. **Cholecystostomy** is an incomplete operation and accounts for many secondary operative procedures. However, it is preferable to a cholecystectomy in which there is traumatism to the common duct. Complications increase more than proportionately with the duration of the disease, and curability becomes less possible the longer primary surgical intervention is delayed.

**Symptoms Following Cholecystectomy**—MacDonald<sup>46</sup> feels that persistent symptoms following cholecystectomy, or other biliary tract surgery, is a neglected subject, which requires more accurate follow-up study in order to evaluate this important phase of biliary tract disease. He groups the patients under two headings — “Minor Complaints” and “Major Complaints.” A small number of patients will have symptoms of varying severity, and of either major or minor importance following operation for a short period. These complaints usually subside. Only if they persist or reappear do they constitute the so-called and poorly named, postcholecystectomy syndrome. Thoughtful and carefully supervised treatment and adequate postoperative care will relieve all but the serious surgical cases. Among the temporary or nonoperative causes of post-

operative discomfort, or pain which should be considered are: Sphincter spasm; pylorospasm; blood, mucus, or debris in the ductal system; liver or gut trauma; and a T-tube producing common duct irritation or obstruction. Many of these troubles could be prevented if we would realize that they may occur. Prevention is better than cure. The longer after operation that symptoms appear, and the longer they last, the more serious do they become, and the more likely they are to be organic in origin. Symptoms occurring 15 to 20 years later are not likely to be due to calculus disease. If a T-tube is in place, it can often, but not always, be determined by a cholangiogram, whether such symptoms are due to ductal obstruction and if so the type and location of the lesion. Thirty-five per cent diodrast has been found to be the best contrast medium.

The group with major complaint can be tabulated as follows: (1) Wrong diagnosis; (2) residual disease; (3) calculi in the common duct; (4) common duct stricture; (5) partial or intermittent obstruction of the common duct or duodenum; (6) functional disturbances; (7) lack of, or indifference to, medical treatment; (8) traumatic neuroma in the wound; (9) malignancy. The incorrect diagnosis should be averted by accurate history and preoperative studies in order to establish a definite diagnosis. Patients with so-called irritable or spastic colons constitute one of the diagnostic problems. These are relieved by close attention to normal bowel function. The next most common error is related to heart disease, peptic ulcer, kidney or ureteral disorders. Hydronephrosis, urinary calculus, pyelitis, or a stricture of the ureter, with or without normal urine are usual culprits although a ureteral stricture is more commonly the cause of appendiceal-like complaints. Other un-

common conditions which have to be considered are gastritis, pancreatic disease, diaphragmatic hernia, esophageal disease, food allergy, and diseases of the liver. These can present almost any picture resembling indigestion. Functional changes which may enter in differential diagnosis are duodenal or pyloric spasm, "nervous indigestion," and gastric neurosis.

Residual disease is usually concerned with and confined to the biliary tract. It consists principally of hepatitis, pancreatitis, ductal calculi, sphincter imbalance, cholelithiasis, and cholangitis, all of which are capable of producing moderate to severe clinical complaints. These are complications of or resultant conditions of, biliary disease, and probably should be grouped under incomplete diagnosis or wrong diagnosis rather than residual disease, because they were part of the original disease for which operation was undertaken. Stones in the common duct may be overlooked at the time of cholecystectomy. The importance of looking for stones in the common duct at the time of the original operation is emphasized. The insertion of a small catheter in the cystic duct at operation, in those patients whose common duct was not explored, is suggested. This allows every patient to have a cholangiogram made before leaving the hospital, and if stones are present they can be removed. Thus no patient leaves the hospital with stones remaining in the common duct. This procedure is safer and easier for both the patient and the operator and one does not have to wait years before a diagnosis of stones in the common duct is made. Artefacts are easily recognized in all common duct x-ray studies. Finding of cholesterol crystals or calcium bilirubinate is almost sure proof that stones have been over-

looked. The stasis resulting from stricture may often give the same findings.

The differential diagnosis between stone and stricture of the common duct is not as important as a realization that serious ductal disease is present, and that this will usually be progressive, leading to advanced liver disease and finally liver failure. The only treatment is *expert surgery*. A stone is not uncommonly left in the cystic duct stump and this is capable of producing postoperative colic, but it is a rare cause of postoperative complaint compared to the incidence of common duct obstruction. Occasionally stones may roll down from the intra- or extra hepatic ducts. Débris, sand, gravel, clot, etc., are capable of performing a nucleus of a duct calculus if the immediate postoperative drainage is of short duration. Prevention of such symptoms is most desirable and prolonged biliary perfusion with heated fluids should prove itself of more value in this respect than the short lived and often inadequate T-tube drainage. It is not reasonable to expect that a disease which has often been progressive for years will completely disappear in 12 to 14 days, which is the average length of time if T-tube or catheter is left in the common duct.

Eighty to 90 per cent of the cases of common duct stricture are traumatic in origin and the direct result of cholecystectomy. Fortunately, this is not common nor is it uncommon and it is always a possibility. It must be considered in every case having symptoms following cholecystectomy. The time interval between the operation and the appearance of symptoms is of some diagnostic value in determining whether a stricture is due to technical faults, ligature, etc., or inflammatory changes. Pain or dyspepsia may be the only symptoms; however, a persistent biliary fistula should always

TABLE III

ANALYSIS OF 412 GALLBLADDER CASES WITH REFERENCE TO INCIDENCE OF POSTOPERATIVE HERNIA\*

	Patients	Operations	Hernia	Percentage
Right rectus splitting incision :				
Acute cholecystostomy.....	24	...	6	25
Acute cholecystectomy.....	25	...	4	16
Chronic cholecystostomy.....	3	...	0	0
Chronic cholecystectomy.....	263	...	29	11
Transverse incision:				
Acute cholecystostomy.....	1	...	0	0
Acute cholecystectomy.....	3	...	0	0
Chronic cholecystostomy.....	0	...	0	0
Chronic cholecystectomy.....	28	...	3	10.7
Oblique or subcostal incision:				
Chronic cholecystectomy.....	16	...	0	0
Kammerer incision:				
Acute cholecystectomy.....	1	...	1	100
Chronic cholecystectomy.....	18	...	4	22.2
Reverse Kammerer incision:				
Chronic cholecystectomy.....	7	...	2	28.5
Right angle incision:				
Acute cholecystectomy.....	1	...	0	0
Chronic cholecystectomy.....	3	...	2	66
	393	393	51	12.9
Double operations:				
Acute cholecystostomy followed by acute or chronic cholecystectomy.....	19	38	8	21
	412	431	59	14.3

\* G. A. Carlucci: Am. J. Surg.

be suspected of being due to an obstruction of the common duct. Jaundice, chills, fever, etc., may or may not be present. Partial obstruction of the common duct or duodenum may occur if the surface is not early peritonealized, and adhesions follow. Kinking of any segment of either may produce obstructive symptoms of varying severity. Adhesions may also interfere with normal functions of the pylorus. This is one of the few places where abdominal surgery, with relief of adhesions, will relieve symptoms. The importance of an improper diet postoperatively is emphasized as one of the causes of persistent pain. Therefore medical treatment should not be neglected following operation.

Traumatic neuroma of the abdominal wall may follow any incision. It may produce pain in the operative scar region. If the pain is severe or persistent surgical removal may be indicated. Cancer of the biliary tract is not uncommon. It constitutes 0.5 per cent of the abdominal malignancy and should always be considered both pre- and post-operatively. It is not an uncommon cause of post-cholecystectomy complaints. Diagnosis is possible but not probable. All gallbladders should be examined pathologically in order to rule out malignancy. Malignant changes are earliest seen in the fundus and near the cystic duct, although they may occur at any time. The liver is involved usually early and

jaundice is present soon after. Impartial liver involvement is due partly to enlarged glandular pressure on the hepatic or common duct.

An analytical study of 412 patients with gallbladder disease, both acute and chronic, was presented by Carlucci.<sup>47</sup> The incidence of hernias found in this

fairly strong and less apt to bulge. In the author's opinion, these two incisions should be the ones of preference in subacute and chronic cases. Wound infection apparently doubles the incidence of abdominal hernia. Patients with pulmonary complications are twice as apt to get a hernia as patients without respira-

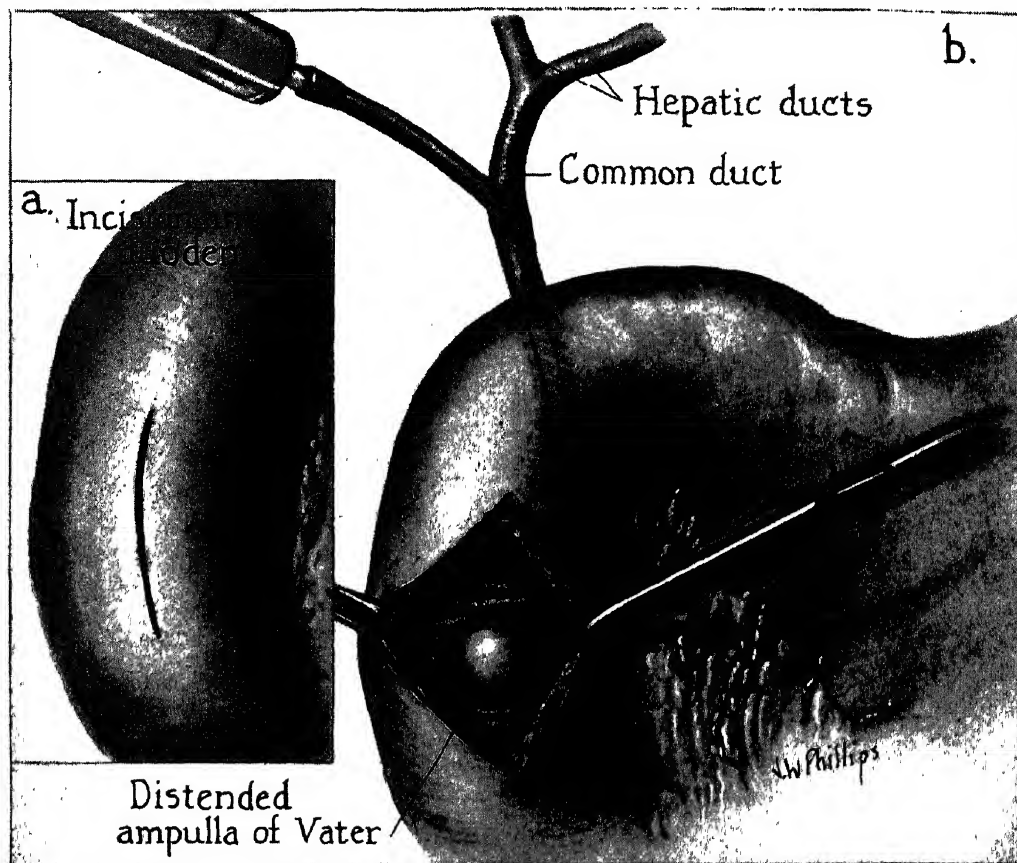


Fig. 8—A, Shows site of incision in the duodenum to expose the opening of the common duct. B, Showing site of insertion of catheter to irrigate the common duct. (J. E. Strode: Ann. Surg.)

series may be easily seen from Table III. Despite the fairly large group of cases studied, no definite conclusion could be arrived at as to the relative value of the incision used in relation to postoperative hernia, due to the fact that there was such a large number of operations done through a split rectus incision, and relatively few done through other incisions. It seems apparent, however, even with a small series that the subcostal or transverse incision leaves the abdominal wall

tory symptoms. Pregnancy apparently had no deleterious effect on wound healing. It was not possible to make a survey of the different comparative value of silk and catgut.

**Biliary Dyskinesia**—Gray and Sharpe<sup>48</sup> point out that biliary dyskinesia is a distressing problem. The two most probable causes of its occurrence are: (1) The erroneous diagnosis of cholecystitis and ill advised removal of the gallbladder, with the persistence of

some functional disorder of the chole-dophis sphincter, and (2) residual inflammatory disease of the liver, pancreas, or ductal system. The possibility that some inflammatory or mechanical lesion of the cystic duct may cause typical symptoms of cholecystic disease suggests that a similar lesion in a remnant of

eration, in which the cystic duct, with or without stones, is removed.

In a series of 44 cases, all specimens of cystic duct removed showed evidence of disease; in 35 cases (79 per cent) there was marked evidence of recent inflammation. In 26 cases of biliary dyskinesia, in which at second operation

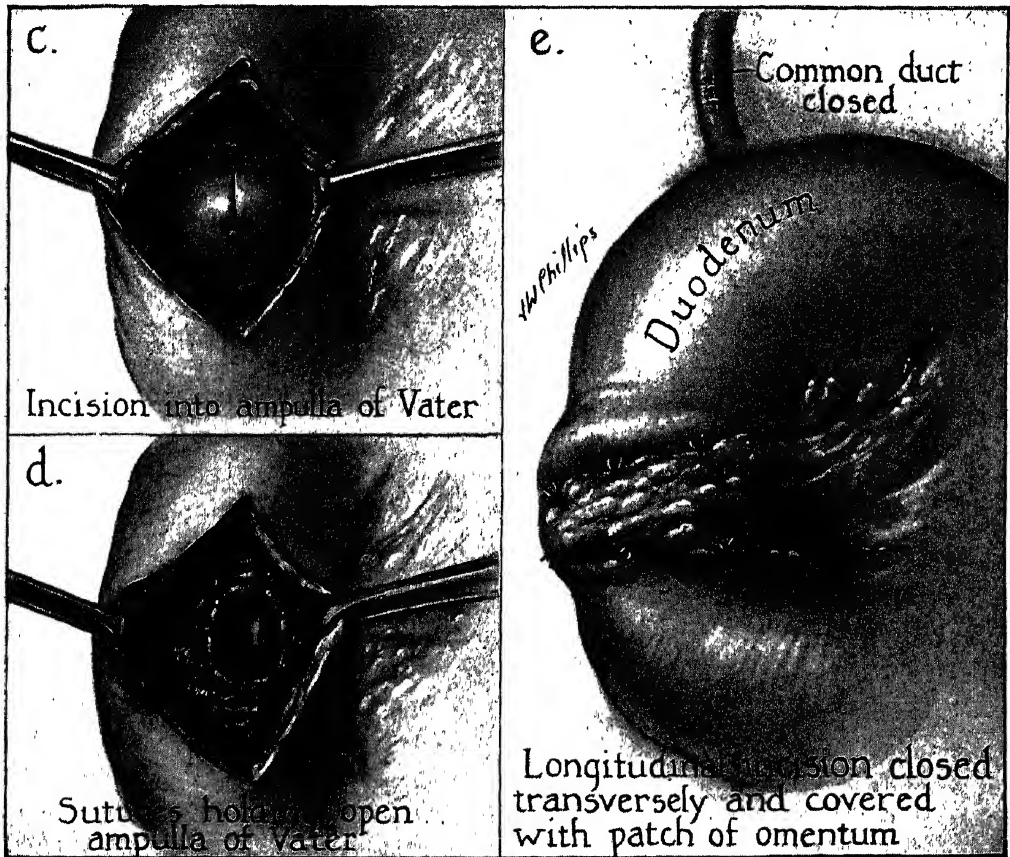


Fig. 9—C, Showing the incision into the ampulla of Vater. D, Showing the technic of procedure of holding open the ampulla of Vater. E, Showing the method of protection of the incision into the duodenum. (J. E. Strobe: Ann. Surg.)

cystic duct may be the obscure cause of persistent postcholecystectomy pain. In many cases the removal of this remnant of the cystic duct has been coincident with choledochostomy and choledocholithectomy. If the original operation was performed on the basis of adequate historical and roentgenographic indications, or both, about 70 per cent of such patients have been found to obtain relief of persistent symptoms by the second op-

only a remnant of the cystic duct was removed, approximately 65 per cent were relieved of their symptoms, provided the first operation had been well advised and necessary. If the first operation was performed on the basis of inadequate indications, 100 per cent failure resulted from the secondary operations in which only drainage of the common duct or removal of a remnant of the cystic duct was accomplished. The importance of



operating only for adequate disease of the biliary tract is emphasized. Meticulous care to avoid damage to the common bile duct, but at the same time removing the cystic duct, must be exercised. The cystic duct remnant should always be looked for in secondary operations.

Strode<sup>49</sup> points out that symptoms of biliary colic can, and do, occur in the absence of gallstones. Biliary dyskinesia must be thought of when no stones are found at exploration. Dyskinesia of the biliary passage is a disease entity with which the medical profession should become more familiar. He discusses various phases of biliary tract physiology and various pathological changes due to gallstones which may produce symptoms following cholecystectomy. Two cases are presented showing the symptom complex and relief by operations described.

The first case was a woman, who first came under his care in 1928 due to gallbladder colic, which had been intermittent for from 15 to 20 years. There had never been fever, chills, or jaundice. At operation, in 1932, a gallbladder containing one large stone and several smaller ones was removed. The common duct was palpated, but not explored. Twelve days after this operation pain recurred, requiring 0.03 Gm. ( $\frac{1}{2}$  grain) of *morphine* for relief. These attacks occurred repeatedly until she was operated upon the second time in 1935. The common duct at this time was found to be slightly enlarged, no stones were present, and a rubber catheter could be passed down into the duodenum. Symptoms soon recurred following this operation. The attacks were not relieved by *nitrites* nor was there evidence of jaundice. All other diagnostic studies were normal. In 1942 a third operation was performed. Thorough examination of the biliary ducts failed to reveal any stones. In order not to overlook an impacted stone at the ampulla, a transduodenal incision was made exposing the ampulla. An incision approximately one-half inch in length into a ballooned-out area in the ampulla was made. From this area the common duct was easily irrigated, probed, and scooped without evidence of stones. The opening into the ampulla of Vater was maintained

by interrupted fine chromic catgut sutures. The duodenum was closed transversely with a protecting line of omentum over the suture line. The opening of the common duct was closed with interrupted chromic catgut sutures. The patient made an uneventful recovery and was entirely free of symptoms eight months following this operation.

The second case, a 48-year-old female, who had suffered for 20 years with recurrent severe attacks of epigastric pain, was subjected to cholecystectomy and palpatory exploration of the common duct in June, 1942. On the second day after operation similar pain recurred and the patient suffered from excruciating attacks of pain similar to that experienced before operation. These attacks required repeated injections of large amounts of *morphine* for their relief. At no time was there clinical evidence of jaundice. Exploration of the common duct was undertaken on June 2, 1942. The duct was not noticeably enlarged. No stones could be found. Fluid could not be made to pass into the duodenum. A transduodenal exploration with division of the ampulla, including the sphincter of Oddi, was performed. No stones were found. The incision through the sphincter area was not closed in this case. The duodenum was closed in a transverse manner as described in the other case. Convalescence was uneventful. The patient left the hospital on the twelfth day after operation. She has remained asymptomatic for four months.

The operations, which were discussed for relief of biliary dyskinesia, include: *Removal of the gallbladder with prolonged drainage of the common duct by means of a T-tube; dilating the ampulla of Vater*, with sounds of increasing size (danger of retroperitoneal infection due to injuries of the duct); *choledochoduodenostomy*, followed by *gastroenterostomy*; *removal of a portion of the sphincter area* by means of a sphinctertome, which is dangerous due to blind operation. The author feels that the *transduodenal exploration with subsequent division of sphincter of Oddi* is the only procedure that lends itself to arriving at a correct diagnosis. It permits a direct visual attack on the seat of the trouble and if a stone is pres-



ent this may be removed, thus avoiding undesirable and unnecessary sidetracking operation.

**Treatment of Biliary Colic**—Best and Barr<sup>50</sup> carried out a series of experiments on the problem of relieving biliary colic. *Antispasmodic drugs*, which would consistently relax the wall of the gallbladder, the region of the cystic duct, and the sphincter area at the lower end of the common duct, would not only hasten and prolong the relief that came by the necessary *morphine*, but might also prevent further extension of the pathological process by permitting free drainage of the biliary tract. With an intact gallbladder, biliary pain is most frequently due to increase in pressure within the gallbladder. With a pathological gallbladder, the choledochosphincter may or may not be in a spastic state, causing increased pressure in the biliary ducts which would also contribute to the pain. *Atropine* could be indicated, as at times it definitely relaxes the sphincter area or at least raises its threshold of irritability. A spastic state of the choledochosphincter may be contributing to the pain accompanying the gallbladder colic; *morphine* hypodermically and *glycerol trinitrate* orally should be tried 30 minutes to a few hours later if the *morphine-atropine combination* has not given relief. Either atropine or glycerol trinitrate should be given with morphine to help counteract the tone or spasm stimulating effect of morphine on the intrabiliary pressure. For patients who have had a previous cholecystectomy, the morphine and glycerol trinitrate combination should be tried first for biliary colic. If it does not afford relief a morphine-atropine injection should be given. Probably the morphine-atropine combination should be tried first for patients with an impacted stone of the gall-

bladder and then the atropine with glycerol trinitrate alternately every four hours. Morphine should be used in the four-hour intervals only as needed. This may be continued for several days in hope that the cystic duct will become sufficiently relaxed to permit egress of fixed bile from the gallbladder into the common duct, and then the sphincter of Oddi would be sufficiently relaxed to permit the bile to pass through the duodenum. When the gallbladder has been removed, the morphine-glycerol trinitrate combination is most apt to give relief. The glycerol trinitrate is then alternated with atropine every four hours for several days and morphine is added as necessary. In their experiments, *depropanex* was not found to be as efficient as either morphine or nitroglycerin in the management of biliary colic. *Trasentin* seems to have qualities similar to atropine, but probably not as reliable, yet at times it may be of advantage in the treatment of biliary colic.

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## LIVER

FREDERICK A. FISKE, B.S., M.D., F.A.C.S.

### Trauma

Pilcher<sup>1</sup> points out that massive rupture of the liver is one of the most serious abdominal injuries usually resulting from blunt trauma. Most of the cases end fatally within a few hours, due to hemorrhage and shock; a few, who do survive the initial hemorrhage, die later from bile peritonitis or intestinal obstruction; reported cases of recovery are rare.

He was able to find only three cases of recovery following massive rupture of the liver in recent literature. To these he adds a fourth case, which recovered following massive rupture of the liver, complicated by a triple rupture of the right kidney. The massive rupture of the liver was satisfactorily repaired with

only three interrupted No. 2 chromic catgut sutures. While a gauze pack above and below the liver surface was used, it was felt that cigarette drains would have been better than the gauze packs. The right kidney was also removed at operation.

Postoperatively, there was very little oozing of blood and the amount of bile drainage was very slight, ceasing entirely on the tenth day. There was no jaundice. *Vitamin K* was administered for one week as a prophylactic measure. This showed that when lacerated liver tissue is accurately approximated, the ruptured bile sinuses and blood vessels heal rapidly. Infection was one of the outstanding postoperative complications. The author felt that the immediate use

of *sulfanilamide* locally and *sulfadiazine* by mouth from the beginning may have prevented this complication. The other important serious postoperative complication was an intestinal obstruction due to the amount of gauze packing, which was placed between the liver and duodenum. It was pointed out that large gauze packs are at best a crude and primitive form of treatment, and while they may be lifesaving procedures, they must frequently be considered as a confession of lack of surgical judgment. It was pointed out that other authors had experienced the complication of intestinal obstruction due to large gauze packs being placed against the duodenum and the undersurface of the liver. On the thirteenth postoperative day evisceration of the small intestine occurred. This was treated by resuturing. Another operation was performed four and one-half weeks after the first operation. It consisted of liberation of the adherent jejunal loops and a jejunostomy. Four weeks after this operation the patient was discharged. Patient has remained well for six months and at the present time is back at work.

This case indicates that massive rupture of the liver should not be considered a surgical defeat. Treatment should consist of *suturing the laceration together, avoiding massive gauze packs*, and depending upon nature's power of healing to close the traumatic rupture.

Some interesting clinical, physiologic, and biochemical observations made on a healthy young adult male patient, who received an injury limited to the liver, are reported by McCorkle and Howard.<sup>2</sup>

A male, aged 30, injured in an automobile accident, was admitted to the hospital in shock, associated with lacerations and abrasions of the face and the mouth, marked tenderness, guarding of the upper right abdomen, and decreased peristalsis. After an intravenous infusion of 1,000 cc. of glucose and transfusion of 1,500 cc.

of citrated blood, the patient showed evidences of hemoconcentration, and, due to continued abdominal signs, a laparotomy was performed. At operation a 10-cm. laceration was felt in the dome of the right lobe of the liver. Bleeding was controlled by a hot compress, while the remainder of the abdomen was explored. Since bleeding had ceased during the exploration a Penrose drain was inserted to the lacerated area. The day following operation, the patient was weak, pulse uncountable, blood pressure 88/55, and in the afternoon he became wildly delirious with a temperature reaching 107.8° F. This was associated with an oliguria and azotemia. *Parenteral fluids, glucose, and physiologic saline* were given and *continuous oxygen inhalation therapy* provided. Three transfusions of 500 cc. of *citrated whole blood* were given in a period of several hours; sedation by *paraldehyde*; there was a gradual decline in temperature. The patient gradually became less restless and showed a diminishing coma for the first two days, and then became mentally clear. The hypotension, oliguria, and azotemia decreased rapidly. The abdomen remained soft without distention throughout the postoperative course. There was mild icterus up to 38 units, which gradually subsided to 12 units on the fifth postoperative day. The prothrombin time was estimated at 80 per cent of normal on the third day and 100 per cent on the fifth day. Recovery followed a stormy course for the first 4 days.

Discussing this case, the author points out that crushing or gunshot injuries of the liver may be manifested by: hyperpyrexia; alterations in the blood chemistry, which appear early and consist chiefly of an increase in the nonprotein nitrogen and creatin; tachycardia; restlessness, collapse, and delirium; and oliguria or anuria associated with red blood cells, white blood cells, casts, and albumin in the urine. The usual liver function tests are impossible to perform early in the course of the disease due to the oliguria and the critical condition of the patient. Pathological changes in the liver of patients who have died of the traumatic "hepatorenal syndrome" are said to be degenerative, consisting of edema and necrosis, and to be confined prin-

cipally to the cellular portions of the traumatized regions. Diffuse degenerative renal lesions have been described and are usually regarded from the convoluted tubules. The explanations are variously quoted as being due to a toxic product, abnormal disturbances in physiology associated with shock, dehydration, alkalosis, hyponitremia, hypochloremia, or the roll of anaphylaxis and infection. Active treatment of shock with *transfusions of blood*, or *plasma* given repeatedly and in large amounts is necessary to replace lost blood and restore the blood protein level. Prevention of anoxemia by continual administration of *oxygen* is also important. *Glucose* is extremely important. The use of *chlorides* should be determined by the degree of loss in chlorides. The use of *dehydrocholic acid therapy* may be important in stimulating the function of a depressed liver. This may also improve kidney function. *Operative therapy* directed at control of the hemorrhage must be carried out at the optimum time, which is determined by the response to treatment for shock.

An anesthetic agent should be selected with the idea of providing adequate oxygenation. The operation should be as rapid and gentle as possible. The question of suturing, packing, or resecting a damaged portion of the liver must be decided in the individual cases. Suturing is preferred; packing should be avoided if possible. *Thrombin spray* may be beneficial in controlling the hemorrhage.

### Liver Deaths

Heyd<sup>8</sup> points out that there are three types of death which follow gallbladder surgery:

1. Liver deaths associated with hyperpyrexia and coma. Death ensues in 18 to 36 hours. In this group the patients are usually obese with a history of

chronic gallbladder disease, having apparently simple gallbladder operations without preoperative contraindications to surgical intervention. Following cholecystectomy, recovery from anesthesia is slow, and the patient never does fully react from the anesthetic. In 4 to 6 hours, the patient is in a semicomatose state that rapidly passes into stupor and coma with a rapidly ascending temperature up to 105° or 106° F.

2. Liver deaths associated with a constantly diminishing jaundice and a secondary development of stupor and coma show a final clinical picture similar to "cholemic death" of cirrhosis of the liver. These patients have had a severe type of biliary duct infection with obstructive jaundice and frequently have had a previous cholecystectomy. A common duct obstruction had been relieved by drainage. The postoperative condition of the patient has been somewhat, but not completely, satisfactory. After a variable period, four to seven days, the patient falls into a stupor, oliguria develops, and the patient dies in coma with hyperpyrexia.

3. Liver deaths associated with and complicated by a secondary renal degeneration of a severe degree. The patients in this group have had a chronic, severe type of gallbladder and duct disease. Underlying, there was an absence of hyperpyrexia and coma. There was a distinct vasomotor collapse 48 hours after operation, and a continuous and increasing degree of oliguria with a pronounced elevation of the nonprotein nitrogen. Anuria finally dominated the clinical picture with death. This is the group known as the hepaticorenal syndrome.

While the phenomenon of liver deaths is not completely understood, the author felt that while the liver has the most extraordinary ability to protect the or-

ganism from injury arising from the gastrointestinal tract, or from injury coming to it by the systemic circulation, it does not have the same ability to protect itself from necrosis of its own liver cells, and the absorption of the by-products of liver necrosis will lead to death in a relatively short time, without evidence of kidney complications as those stated in the first group, but with kidney complications if sufficient time elapses for these complications to develop.

### Liver Function Tests

Mateer *et al.*<sup>4</sup> point out that liver function tests offer valuable aid in the evaluation of hepatic cell function. However, these tests should be considered as only an aid to clinical and other laboratory findings in making an exact diagnosis. While all tests may show impaired function, frequently these tests do not overlap, because various functions of the liver are not injured equally under different conditions. It is, therefore, advisable to perform several different types of hepatic function tests in order to demonstrate impaired liver function in the greatest percentage of patients with liver damage.

In order to establish normal standards for each test and determine the sensitivity and reliability of each test, 40 normal adults ranging from 25 to 35 years of age were studied with the following results: (1) The cephalin cholesterol flocculation test is reliable only if an unripened cephalin is used; the 1 plus tests are regarded within normal limits, and positive diagnostic importance is attached only to 2 plus, 3 plus, and 4 plus. Ripened cephalin gives numerous false positive results, whereas unripened cephalin yielded only 12.5 per cent of false positive results.

The Quick intravenous hippuric acid method corroborated Quick's statement that any urinary output of less than 0.70

Gm. of benzoic acid as hippuric acid in the one-hour urine specimen indicates some degree of impairment of hepatic function.

The modified serial 2 mg. per kilogram bromsulphalein method revealed the fact that 20 minutes is the normal time for complete disappearance of the dye from the blood stream with this dosage. Therefore, if one wishes to use only a single blood specimen, it should be taken at the end of 20 minutes rather than 30 minutes.

Comparing these tests with the older liver function tests, *viz.*, the old hippuric acid tests and the Rosenthal bromsulphalein method (2 mg. doses of dye administered and a single blood specimen withdrawn 30 minutes later), the following results were found: The intravenous hippuric acid test yielded 85 per cent more positive tests than the old hippuric acid tests. The serial bromsulphalein method, using the 2 mg. per kilogram dose of the dye, and 20 minutes as the normal clearance time for the dye, yielded 100 per cent more positive tests than the 30-minute Rosenthal bromsulphalein method. The cephalin test yielded exactly the same number of positive tests as the intravenous hippuric acid test, but yields 33 per cent more positive tests than the serial bromsulphalein test.

A study of the relative sensitivity of these tests in various pathological groups of cases indicates that the four new tests are appreciably more sensitive than the two older tests. Of special interest was the observation that in a group of 67 patients with gallstones, studied before operation, 53 per cent yielded a positive intravenous hippuric acid test, 50 per cent a positive cephalin test, and 42 per cent yielded a positive, serial, 20 minute, 2 mg. bromsulphalein test, whereas only 15 per cent yielded a positive Rosenthal bromsulphalein test. *This type of in-*

formation is of great practical value in selecting cases of cholelithiasis needing special preoperative preparation.

A new and improved normal standard for the 5 mg. per kilogram bromsulphalein test was studied on 30 normal individuals and a 45-minute period was adopted as the normal standard for complete disappearance of the dye. As a result of the studies made on the improved bromsulphalein test, it was found to be as sensitive as the cephalin test and the intravenous hippuric acid test when a 45-minute interval was used. It was found that the 5 mg. test was more sensitive than the 2 mg. bromsulphalein method when 20-minute and 45-minute intervals were used.

The only objection to the 5 mg. per kilogram dose of bromsulphalein is that some patients have unpleasant reactions following the injection of this dose. The reaction consists of transient headache, a feeling of faintness, and in some cases a chill. These symptoms occur about 45 to 60 minutes following the injection. No prolonged or unfavorable reactions have been demonstrated. This type of reaction rarely occurs when the smaller dosage is employed, *viz.*, 2 mg. per kilogram.

In cases in which it is desired to determine the presence or absence of a slight degree of impaired liver function, two or three of the most sensitive tests should be employed, *e. g.*, the cephalin test, the 5 mg. per kilogram, 45-minute bromsulphalein test, and the intravenous hippuric acid test. When it is desirable to determine the presence of impaired liver cell function and also obtain from the tests as much information as possible about the degree of impairment, there is an important advantage of using several tests of varying sensitivity, *e. g.*, the very sensitive cephalin test, the 2 mg. per kilogram 20-minute bromsulphalein test

of intermediate sensitivity, and the less sensitive oral hippuric acid test.

In a group of 3788 cases completely studied, serum bilirubin determinations were made in 1835 (48.9 per cent). Using these cases as a basis of study, Johnson and Bockus<sup>5</sup> found that *hyperbilirubinemia* of a moderate degree is frequently encountered in gastrointestinal cases. The cause of hyperbilirubinemia may be obstructive jaundice, hemolytic jaundice, toxic hepatocellular disease, and incipient liver-spleen disease. In a small group of cases idiopathic hyperbilirubinemia must be considered. In this series there were no instances of prolonged delayed hepatic changes associated with persistent hyperbilirubinemia. Serum bilirubin values in excess of 0.5 mg. per 100 cc. of blood were termed hyperbilirubinemia. Hyperbilirubinemia occurred in 18.3 per cent. The distribution of the hyperbilirubinemia values was determined in cases of duodenal ulcer, irritable duodenum, colon disease, miscellaneous disease, liver dysfunction, and obstructive jaundice. The few cases of persistent hyperbilirubinemia followed for years failed to show hematologic or progressive hepatic disease.

Steigman *et al.*<sup>6</sup> give the indications and uses of liver function tests based on an experience gained from an examination and study of 563 jaundiced and 112 nonjaundiced patients. In 111 of these cases which came to operation, the studies were supplemented by histologic and fluorescent microscopic examination of liver biopsy specimens. The usefulness of liver function tests depends upon the presence or absence of jaundice. In jaundice, the usual problem is to decide whether it is obstructive or parenchymatous and whether surgical intervention is indicated. Some liver damage occurs in almost every case of jaundice. In parenchymatous jaundice one may have



an associated obstructive factor. In differentiation between obstructive and parenchymatous jaundice, less sensitive liver function tests are indicated—tests which give positive results only if more severe damage to the liver parenchyma is present. In patients without jaundice, one is most interested in discovering slight deviations of liver function. For such cases, the more sensitive liver function tests are needed.

In order to differentiate between medical and surgical jaundice, attention should be given first to *examination of bile pigment metabolism* before the function tests of the tolerance type are used. Normally, traces of urobilinogen and no bilirubin are excreted in the urine. In hemolytic jaundice more hemobilirubin is being formed. The liver compensates by excreting larger amounts of bilirubin B into the bile. More urobilinogen is formed in the intestines, more is reabsorbed into the blood, and more is excreted into the urine. Thus, in *hemolytic jaundice the urine contains no bilirubin, but increased amounts of urobilinogen*. In jaundice with complete obstruction, the cholobilirubin cannot enter the intestine. No urobilinogen is formed and none absorbed into the blood stream. The bile ducts and capillaries above the obstruction dilate, and the capillaries may finally rupture, permitting regurgitation of cholobilirubin into the blood stream. Thus, cholobilirubin, which can pass through the kidneys, circulates in the blood. *In obstructive jaundice, the urine contains bilirubin but no urobilinogen*. *In partial obstruction*, as is usually found in cholelithiasis after the first few days, *bilirubin is present in the urine while the amount of urobilinogen varies according to the degree of obstruction* and may even be increased after release of the obstruction.

In parenchymatous jaundice, cholobilirubin regurgitates into the blood stream. Early in the disease the greater amount of cholobilirubin reaches the intestines, where urobilinogen is formed. Little of the reabsorbed urobilinogen is oxidized by the impaired liver and much of it appears in the urine. Hence, *in parenchymatous jaundice the urine contains bilirubin and much urobilinogen in the incipient and recovery stages, but only little urobilinogen in the fully advanced stage*.

**Test for Bilirubin in the Urine—**Overlay 2 to 5 cc. of urine with 1:10 alcoholic dilution of tincture of iodine. A green ring forming at the area of contact indicates bilirubin.

**Test for Urobilinogen—**To 2 cc. of freshly voided urine, add 5 to 8 drops of Ehrlich's aldehyde solution. A pink color, increasing as the urine is heated, indicates normal amounts of urobilinogen. An immediate cherry-red color indicates high amounts. A pink color only on heating shows decreased amounts. No color change after heating means absence of urobilinogen. A developing green color is due to bilirubin, which has to be removed by adding equal amounts of lime water and 10 per cent calcium chloride solution to the urine, and then performing the test on the filtrate. Urobilinogen changes to urobilin on standing. The latter does not give the color reaction. Consequently, only fresh urine should be used. It is pointed out that the direct reaction to the Van den Bergh test has the same significance as bilirubin in the urine except in cases of severe kidney insufficiency.

The authors made a correct diagnosis in 62 per cent of the cases studied, when a careful history and physical examination combined with one urinalysis for bilirubin and urobilinogen were performed. The factors concerned with fail-



ure to diagnose the 38 per cent of the cases were: (1) The incomplete obstruction due to stones, which may be associated with secondary hepatitis, or with compensating hypersecretion of bile while the obstruction is open; (2) complete obstruction encountered in certain stages of parenchymatous jaundice, which occurs only in severe hepatitis and usually does not last more than two weeks.

Quantitative measurements of the urobilinogen excretion in 24 hours associated with determination of the urobilinogen in the feces increased the incidence of correct diagnosis to 79 per cent. These studies should be repeated at frequent intervals and a chart of the rise or fall recorded.

In addition, the following tests were useful in differentiating between medical and surgical jaundice:

**Galactose Tolerance Test**—In a normal adult, out of 40 Gm. of galactose ingested, not more than 3 Gm. are excreted by the urine, the remainder being stored in the liver. With impaired liver function, glycogenesis is also impaired and a larger quantity may appear in the urine. Failure of intestinal absorption may be a fallacy in this test. This may be indicated by the presence of sugar in the urine longer than five hours.

**Oral Hippuric Acid Excretion Test**—Ingested sodium benzoate is detoxified by the liver and excreted in the urine as hippuric acid. A normal liver detoxifies enough of the 5.9 Gm. so that hippuric acid, equivalent to more than 3 Gm. of sodium benzoate, appears in the urine. In the presence of renal insufficiency, this test is of doubtful value; however, disturbed intestinal absorption will not make the results appear normal.

**Cephalin - cholesterol Flocculation Test**—The liver influences the concentration of plasma proteins and the constitution of the plasma globulin. In liver

damage, the concentration of plasma albumin decreases while the globulin may remain unchanged or actually increased. The normal albumin-globulin ratio of the plasma is 2:1; it may be changed in chronic liver damage to 1:1 or even become reversed. The following tests indicate changes in the plasma globulin: (1) Cephalin-cholesterol flocculation test in which pathologic globulins flocculate a cephalin-cholesterol emulsion in various degrees; (2) the colloidal gold test; (3) the Takata-Ara test, in which the globulins flocculate an alkaline sublimate solution in serial dilutions. The *early globulin changes in acute hepatitis can be elicited by the cephalin-cholesterol flocculation test and by the colloidal gold test*. The Takata-Ara test becomes positive only in chronic liver disease. It is pointed out that false positives may occur in the cephalin-flocculation test.

**Blood Phosphatase Test**—Alkaline phosphatase is an enzyme which splits organic phosphorus compounds in an alkaline medium to inorganic phosphates. It is produced by osteoblasts and consequently it is increased in bone diseases. It is probably excreted through the bile and hence increases in the blood in disturbances of biliary excretion, as seen in extrahepatic obstruction or intrahepatic block of parenchymatous jaundice. A high blood phosphatase level with a high degree of flocculation speaks for hepatitis, while with a low degree of flocculation an uncomplicated extrahepatic obstruction is probable.

**Duodenal Drainage**—This will reveal the presence or absence of bile in the duodenum and the character of bile if obtained. The microscopic examination of the sediment, showing pus cells in the liver bile, indicates a cholangitis; pus cells in gallbladder bile, a suppurative cholecystitis (empyema); cholesterol, calcium carbonate, and bilirubin crys-

tals particularly in gallbladder bile speaks for cholelithiasis. In addition, the excretory function of the liver for dyes can be tested during duodenal drainage by injecting azorubin S. Normally, a red coloration of the bile appears within 25 to 30 minutes after the injection of 4 cc. of a 1 per cent solution intravenously.

By the addition of these liver function tests, the correct diagnosis was increased from 79 per cent to 95 per cent. The chief cause for failure to make the diagnosis in these 5 per cent was due to the patients having an obstructive jaundice first, and coming under observation at a time when secondary hepatitis had already developed. Therefore, improvement in liver function tests does not add substantially to the increased differentiation between medical and surgical jaundice.

*The following tests point to liver breakdown and should be treated by immediate surgery in cases of obstructive jaundice.*

**1. Increase of the Icteric Index—**In obstructive jaundice, the urinary excretion of bilirubin removes much of the regurgitated bilirubin. Thus, after a while a fairly constant bilirubinemia results at an icteric index of 100 to 150. In parenchymatous jaundice, the associated kidney damage reduces the urinary excretion of bilirubin with consequently higher and rising icteric indices. A sudden rise of a fairly constant level points to secondary parenchymatous complications.

**2. Falling Prothrombin Level During Administration of Vitamin K—**In jaundice, intestinal absorption of vitamin K is interfered with, owing to the lack of bile acids in the intestines. In liver damage, the storage of vitamin K in the liver is additionally impaired. Both factors cause prothrombin deficiency, which may be corrected by the administration of vitamin K. In liver damage,

however, the formation of prothrombin even in the presence of vitamin K is not normal. Therefore, after administering vitamin K to a jaundiced patient the consequent rise of the prothrombin level is prompt and prolonged if the liver is undamaged, whereas in cases of liver damage the rise is only slight and is not sustained. Therefore, if a jaundiced patient under observation shows a fall in prothrombin level, or hemorrhagic diastasis appears, secondary liver damage has developed.

**3. Increase of Nonprotein Nitrogen in the Blood—**The nonprotein nitrogen level of the blood rises in parenchymatous liver damage partly because of increased protein breakdown and more so because of associated pathologic changes in the kidneys. The latter is probably on the basis of inability of the damaged tubular cells to prevent urea reabsorption. Therefore, a sudden rise in nonprotein nitrogen is an alarm signal.

4. If, on repetition of the galactose tolerance test and the hippuric acid test, one finds abnormal results with previous normals, the indication is an associated hepatitis.

**5. Millon's Test—**In severe liver damage, increased amounts of amino acids may be present in the blood and thus tyrosine appears in the urine, which is recognized by Millon's reaction. Equal amounts of urine and Millon's solution are boiled and a red color in the supernatant fluid indicates tyrosine. In cases of albuminuria, the protein must be removed to avoid splitting off of the tyrosine.

The degree of liver damage in patients with jaundice is determined by:

**1. Hippuric Acid Excretion Tests—**The amount of hippuric acid excreted is to a certain extent inversely proportional to the degree of liver damage.

**2. Cholesterol-Cholesterol Ester Ratio**—Cholesterol is excreted with the bile; consequently, in biliary obstruction the total cholesterol of the blood rises. Supposedly only the liver cells are able to esterify free cholesterol into cholesterol esters. In the presence of a normal liver, two-thirds of the total cholesterol in the blood is in ester form, a ratio of 1:2. In liver damage, the esterification is impaired and consequently independent of the height of the total cholesterol; the ratio is changed to 1:1 or less than 1. The disturbance of this ratio is more pronounced in greater degree of liver damage.

**3. The Albumin-Globulin Ratio**—The degree of reversal of the albumin-globulin ratio depends on the degree of liver damage, but to a certain extent on the development of ascites as well. This test is of value in follow-up cases of cirrhosis.

**4. The Cephalin-Cholesterol Flocculation Test**—The degree of flocculation varies directly with the degree of liver damage.

**5. Takata-Ara Test**—In chronic liver disease, the variations in the number of test tubes showing precipitation is in direct proportion to the degree of liver damage.

The signs of alarm (liver failure) are: (1) Rise of the icteric index; (2) Milon's test becomes positive; (3) drop in prothrombin level only partly relieved by the administration of vitamin K; (4) drop in cholesterol esters; (5) rise of nonprotein nitrogen.

The signs of recovery are: (1) Rise of the urinary urobilinogen in the face of a decrease in the bilirubinuria; (2) rise in the cholesterol esters; (3) increased diuresis.

In the absence of jaundice, slight changes in the liver function from nor-

mal may be significant. Thus, the more sensitive liver function tests are indicated. The four most common situations in which these tests are useful are:

(a) *Early Cirrhosis*—Slight impairment of liver function may be suspected with:

1. An increased icteric index.
2. Increased urobilinogen in the urine.
3. Bromsulphalein retention.
4. Low albumin fraction and reversed albumin-globulin ratio.
5. Positive Takata-Ara tests.
6. Dense flocculation of the cephalin-cholesterol emulsion.
7. Low cholesterol esters.

(b) *Chronic Gallbladder Disease*:

1. Increased icterus index.
2. Bromsulphalein retention.
3. Dense flocculation of the cephalin-cholesterol mixture.
4. Decreased hippuric acid excretion.

(c) In controlling the therapy with hepatotoxic drugs such as *arsenicals, cinchophens, sulfonamide compounds, bismuth*, and others. The following tests may indicate liver impairment:

1. Increased urobilinogen in the urine.
2. Bromsulphalein retention.
3. Increased icteric index.
4. Decreased hippuric acid excretion.
5. Dense flocculation of a cephalin-cholesterol emulsion.

(d) *Hyperthyroidism*—In hyperthyroidism, impairment of liver function may parallel the degree of thyrotoxicosis. Some feel that the impairment of the liver function may be more important than a basal metabolic rate. The following tests are suggested in evaluating the degree of liver damage:

1. Galactose tolerance test. In hyperthyroidism there is probably, in addition to liver damage, a faster intestinal absorption rate of galactose, which may raise the urinary excretion.
2. Hippuric acid excretion test.
3. Bromsulphalein test.
4. Cephalin flocculation test. The other tests which have previously been discussed under

jaundice may also prove of value in the cases which are not jaundiced.

Paulson and Wyler<sup>7</sup> studied 25 cases with carcinoma of the stomach or colon, who had no clinical evidence of liver metastasis by the following liver function tests: (1) The hippuric acid test; (2) the bromsulphalein test; (3) the Van den Bergh reaction. A correlation was found to exist between the cases of gross hepatic metastasis as determined at subsequent operation, and the degree of bromsulphalein retention, although individual exceptions occurred. No significant correlation was found between the presence of metastasis and the amount of hippuric acid excreted. However, in all six cases in which no hippuric acid was found, metastases were present. In a control series of 25 patients, of comparable age and general health, the hippuric acid test was performed. Sixteen of these patients showed lowering of the hippuric acid synthesis below the level considered as normal, although in 23 of the 25 cases the bromsulphalein level was entirely within normal limits. It is suggested that extreme delicacy in tests of hepatic function may detract from their value as diagnostic aids, because they too frequently may give abnormal results in cases in which liver damage is slight, and give a relatively unimportant part to the clinical picture. This does not invalidate the serial use of delicate tests in order to follow the course of liver disease and determine the prognosis.

**Plasma Prothrombin** — Andrus and Lord<sup>8</sup> have reviewed the literature and summarized the physiology of plasma prothrombin and its relation to liver function. The use of plasma prothrombin as an index of hepatic function, when its response to vitamin K therapy is determined, compares favorably with other liver function tests.

As a working hypothesis to be applied in any specific instance, they look upon vitamin K-plasma prothrombin relationship in the following manner. Into the final formation of plasma prothrombin there enters an extrinsic factor, vitamin K; an intrinsic factor, bile salts; an absorptive mechanism, the intestinal epithelium, and the liver, which not only stores vitamin K, but from this elaborates prothrombin. Derangement of function, or lack of supply of any of the factors, may lead to lower levels of plasma prothrombin, and hence to the hemorrhagic tendency known to be associated with a wide range of pathological states. The relation of plasma prothrombin to surgical disease was considered under the following headings:

1. **Obstructive Jaundice** — In this condition, regardless of the cause of obstruction to the biliary passages, there results an interference with all fat soluble vitamins of which vitamin K is one. As this continues, the level of the hepatic store of vitamin falls, and there is a concomitant fall in the plasma prothrombin. If the obstruction continues, morphological changes in the liver occur, which are characterized by obstructive biliary cirrhosis. This leads to a diminished capacity of the liver to elaborate plasma prothrombin even in the presence of adequate vitamin K. Hence, the patient with obstructive jaundice is likely to bleed if vitamin K is not administered and, if the disease progresses without relief, to such an extent that hepatic damage is too severe even with vitamin K. The use of vitamin K in obstructive jaundice has reduced the death rate from hemorrhagic diathesis from 50 per cent to 0 in cases where the extrahepatic ducts are involved. As a result of observations on the depressing effect of operations on the plasma prothrombin, it would seem unwise to perform an elective operation on

any patient with a level of plasma prothrombin below 50 per cent, as the critical bleeding level is 25 per cent of normal; hence, allowing 25 per cent for the postoperative fall, there would be no margin of safety unless the plasma prothrombin were 50 per cent of normal or higher preoperatively.

**2. Biliary Fistula**—Here again lack of bile in the intestine leads to poor absorption of the fat-soluble vitamin K, hence to diminished levels of plasma prothrombin. In these cases, the liver damage is less marked and takes longer to appear. The biliary fistula has been shown to improve the prothrombin level.

**3. Hepatic Disease**—Prothrombin is lowered in a variety of diseases of the liver which include cirrhosis, multiple abscesses of the liver, catarrhal jaundice, subacute yellow atrophy, and hepatitis.

**4. Intestinal Disease and Nutritional Deficiency.**

**5. Hemorrhagic Disease of the Newborn** — Low plasma prothrombin time during the first few days following birth has been repeatedly reported. This may be corrected by the administration of vitamin K. There has been much speculation concerning the underlying physiology of hypoprothrombinemia of the newborn, its fall during the first few days of life, and its elevation from the eighth to the tenth day. In Quick's opinion, infants are born with normal level of plasma prothrombin and develop a fall in this substance during the first 48 hours of life due to the fact that there is no reserve of prothrombin in the fetus and to physiologic strain put on the fetus during the first few days of life. The abrupt rise in the second week of life is due to bacterial synthesis of vitamin K in the intestinal tract with subsequent absorption and utilization by the liver for the liberation of prothrombin.

**6. Hyperthyroidism**—Altered anatomy and function of the liver associated with hyperthyroidism have been pointed out by many authors. The changes in the liver vary from widespread acute necrosis, usually central, to chronic patchy parenchymatous hepatitis. In a study of 36 patients of diffuse toxic and toxic nodular goiters, the authors found that the level of plasma prothrombin showed little or no correlation with the preoperative basal metabolic rate for the duration of the disease. On the other hand, it appeared that there was a marked fall in the prothrombin during the immediate postoperative period averaging 15 per cent but amounting to 40 per cent or more in some cases. The lowered levels were seen soon after operation and the normal level was attained only after one week had elapsed. These studies indicate the importance of the liver and the advisability of improving the patient's hepatic function during the preoperative preparation and the immediate postoperative phase.

The therapy of hypoprothrombinemia consists of:

1. Protecting the liver by *high-protein, high-carbohydrate, no fat diet*, with sufficient *vitamin B complex*. Avoiding toxic anesthetic agents and anoxemia.

2. The administration of *vitamin K* by one of the various routes.

3. The use of *whole blood transfusions*, which at best is only temporary, and fresh blood should be used.

Abbott and Holden<sup>9</sup> carried out the prothrombin test on 120 patients, most of whom had hypoprothrombinemia. They administered 4 to 8 mg. of *vitamin K* orally in divided doses over a period of 12 to 18 hours. It was felt that a large dose should be given in order to determine the maximal response to therapy within 24 to 48 hours. It was

shown that patients with relatively severe liver damage do not respond to vitamin K therapy, while patients with obstructions to the common duct practically always respond to adequate therapy. The prothrombin test apparently can help in determination of the severity of liver damage in cases of burns. It is believed that by serial examinations, an early and accurate prognosis can be formulated in such cases.

Owen<sup>10</sup> presented in detail 20 cases in which quantitative prothrombin analyses were correlated with clinical findings. In these cases, the test seems to aid in the diagnosis, and to have prognostic significance. The cases were grouped as follows: (a) Jaundice; (b) hepatomegaly; (c) metastatic malignancy of the liver; (d) hepatic congestion and cardiac failure; (e) miscellaneous. The author feels that the test is quite simple and accurate. It does not have the limitations of other liver function tests, such as the galactose tolerance test, which is positive only during the acute hepatic episodes; the hippuric acid excretion, although reliable, is dependent upon a normal renal function; jaundice reduces the use of the bromsulphalein test. The new tests, such as serum cholesterol, serum phosphatase, serum colloidal gold reaction, are, like the test for prothrombin, awaiting further clinical experience. The degree of response of the plasma prothrombin to the administration of vitamin K is a definite index of liver function.

### Effect of Sulfonamides on the Liver

Kapnick *et al.*<sup>11</sup> point out that two types of injury to the liver resulting from the sulfonamides have been described: (1) Jaundice with evidence of diminishing hepatic function accompanying an acute hemolytic crisis, and (2) hepatitis, as a result of a direct toxic effect. Sixty-eight patients who were receiving sul-

fonamides for infections were studied, the plasma prothrombin test being used to indicate changes in hepatic function. Of these 68 patients, 14 or 21 per cent showed an appreciable increase in the prothrombin time during the course of therapy, while only a few of the latter showed changes in the bromsulphathalein excretion, or in the Van den Bergh reaction. The cases with significant increases in prothrombin were presented in detail.

No change in the prothrombin level was noted in any case receiving 4 Gm. or less of sulfonamides a day. Fever alone did not affect the prothrombin level, nor did insufficient diet. Infection alone may have a hepatotoxic effect, and the severity of the infection seemed to be more significant as a cause of prothrombin depression than did the type of sulfonamide used. Since both infection and the sulfonamides may depress liver function, some tests, such as determination of the plasma prothrombin level, are of value in patients with severe infection. The depression in the prothrombin level did not occur until the drug had been used four to five days in most cases. The drug was stopped as soon as any change in the prothrombin level was noted and shortly thereafter the level returned to normal. In all cases in which *vitamin K* was given parenterally the prothrombin time was normal within 24 hours, which indicated that the liver was able to respond. Due to the precautions taken when these drugs were administered, none of the patients developed jaundice or gave clinical evidence of toxic hepatitis. Since changes in the prothrombin level occur well in advance of the clinical signs of severe liver damage, the Quick test is suggested for routine use, say every three to four days, in seriously ill patients receiving sulfonamide therapy.



According to Machella and Higgins,<sup>12</sup> the majority of cases developing jaundice following sulfanilamide have been due to a hemolytic type. In about 0.6 per cent of the patients who have been treated with *sulfanilamide* the jaundice has been ascribed to hepatitis.

In order to determine the rôle of liver trauma in a patient obtaining *sulfanilamide*, four different types of experiments were conducted: (1) A group of animals in which hepatitis had been induced by means of carbon tetrachloride; (2) a group in which hepatitis was being induced by carbon tetrachloride; (3) a group receiving alcohol; (4) a group in which obstructive jaundice had been induced by ligation of the common duct.

The experiments indicate that the administration of *sulfanilamide* in moderately toxic doses does not increase the damage produced in the liver of a rat by carbon tetrachloride, and that it does not impede regeneration of the liver after hepatitis has been induced by carbon tetrachloride. The liver of the animals that received both carbon tetrachloride and sulfanilamide showed less damage than those in which carbon tetrachloride had been administered alone. This observation is in accord with a recent report that sulfonamide drugs act as protective agents against carbon tetrachloride poisoning. The simultaneous administration of alcohol with sulfanilamide did not result in damage to the hepatic cells. The drug did not produce damage of the hepatic cells of animals that had obstructive jaundice. The livers of all animals that received sulfanilamide were dark brown or black as a result of contained blood discolored by the accumulation of various pigments responsible for cyanosis in animals or human beings receiving this drug. These experiments are in accord with clinical observations

which show that when sulfanilamide and allied compounds are administered to patients who have hepatic damage, there is no apparent significant increase of hepatic dysfunction. However, they do not shed any light on the question why, when patients receive sulfanilamide, hepatitis develops in some cases but not in others.

### Cysts of the Liver

According to Munroe,<sup>13</sup> nonparasitic cysts of the liver may be single or mul-



Fig. 1—Preoperative roentgenogram after barium enema, showing the marked displacement of the colon medially and inferiorly by the large mass occupying the right upper abdomen. As pointed out by Hoffmann, this is a most important sign in the diagnosis of liver cysts. (H. S. Munroe, Jr.: *Ann. Surg.*)

tiples. Multiple cysts may be confined to the liver alone, but more commonly they are associated with cysts of the kidneys, pancreas, spleen, lungs, and brain. Multiple cysts are more common in children than in adults, and may be associated



with other congenital malformations, as harelip, cleft palate, and spina bifida. Solitary nonparasitic cysts are more common in adults. Whether justifiable or not it is customary to differentiate sharply between solitary and multiple nonpara-

mental defects are more common in the female sex.

Solitary cysts are most commonly found at the antero-inferior portion of the right lobe of the liver. The quadrate lobe or the left lobe is sometimes in-

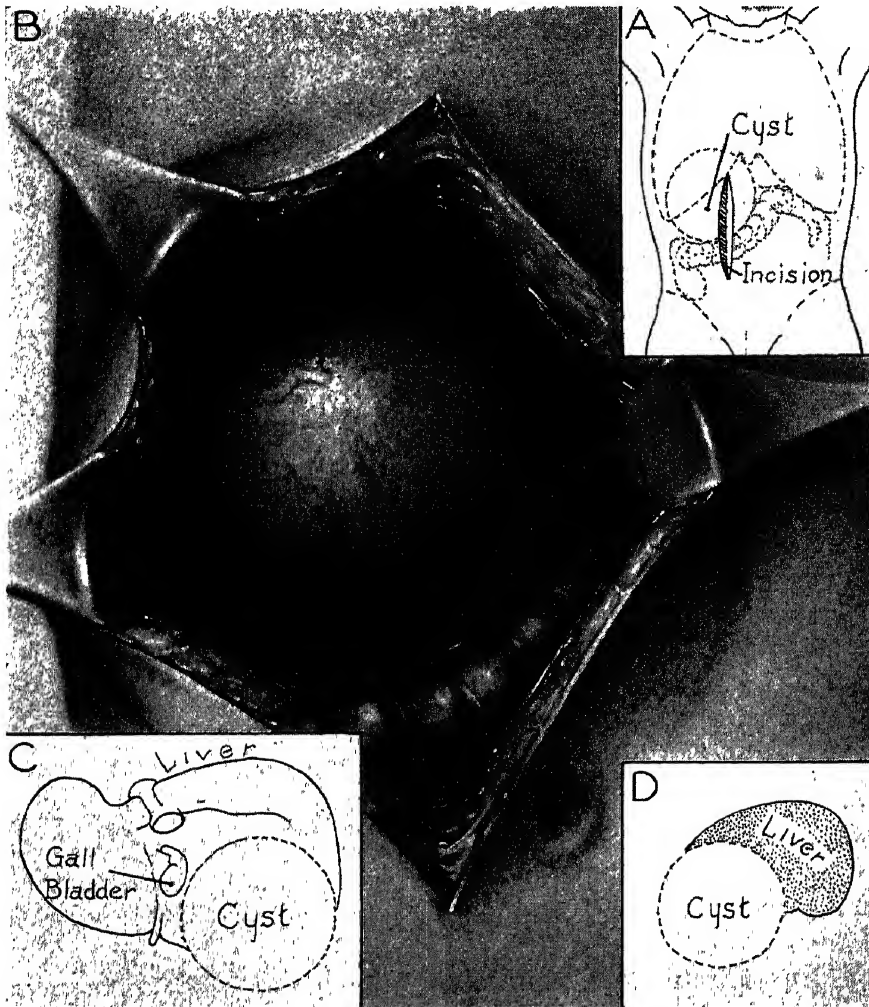


Fig. 2—Appearance and anatomic relationship of the mass upon operative exposure. (H. S. Munroe, Jr.: *Ann. Surg.*)

sitic cysts of the liver. Whether the solitary cyst of the liver is a lone manifestation of polycystic disease or an entirely unrelated process is a debatable issue, and until this is better understood it seems advisable to consider the two conditions as separate entities.

The cysts occur more often in females than males, the ratio being 4:1. The explanation seems to be that develop-

ment, and, in still fewer cases, the cyst occupies the center portion of the liver. The size of the cyst and the amount of liver destruction vary considerably. Some cysts are microscopic, and some may fill the abdomen. An entire lobe of the liver may be destroyed by the cysts. The cyst may be wholly or partially intrahepatic, or it may be pedunculated. Little is known about the growth of these cysts,

but apparently growth is so tardy that, as a rule, the adjacent viscera quickly adapt themselves to the presence without symptoms. In contradistinction to hepatic parasitic cysts, these cysts have a characteristically low internal tension; their external surface is usually smooth, glistening, and grayish-blue, often showing many dilated veins. The appearance may be not unlike that of a smooth-walled cyst of the ovary. The internal surface of the cyst wall is usually smooth, less regular, and usually trabeculated. The thickness of the wall is variable. There is usually no definite line of cleavage between the intrahepatic and partially intrahepatic cyst wall, and the normal liver tissue. The cystic contents vary from clear, watery, sometimes yellowish-brown fluid, neutral or alkaline in reaction, with a specific gravity varying from 1.007 to 1.024, to a semisolid material resembling organized clot.

The most generally accepted classification of nonparasitic cysts of the liver is that of Sonntag: (1) Blood and degenerated cysts; (2) dermoid cysts; (3) lymphatic cysts due to obstruction or to congenital dilatation of the lymphatics; (4) endothelial cysts; (5) cysts due to obstruction of the bile duct; (6) proliferative cysts (cystadenoma). Solitary nonparasitic cysts of the liver apparently grow so slowly that in most instances few, if any, symptoms are produced; advice usually is sought due to the presence of a painless abdominal swelling. There may be a sudden onset of acute symptoms. This is seen when an acute hemorrhage occurs into the cyst, when suppuration supervenes, or when the pedicle becomes twisted in the pedunculated variety. A correct preoperative diagnosis is rarely made, the majority of cases being diagnosed on exploratory celiotomy or at autopsy. The condition is usually symptomless unless complications

occur or the cyst compresses some adjacent structure such as the extrahepatic bile duct or the first portion of the duodenum. With compression there may be acute hepatic pain, nausea, vomiting, or jaundice. As most of these cysts arise from the antero-inferior surface of the right lobe of the liver, clinical examina-

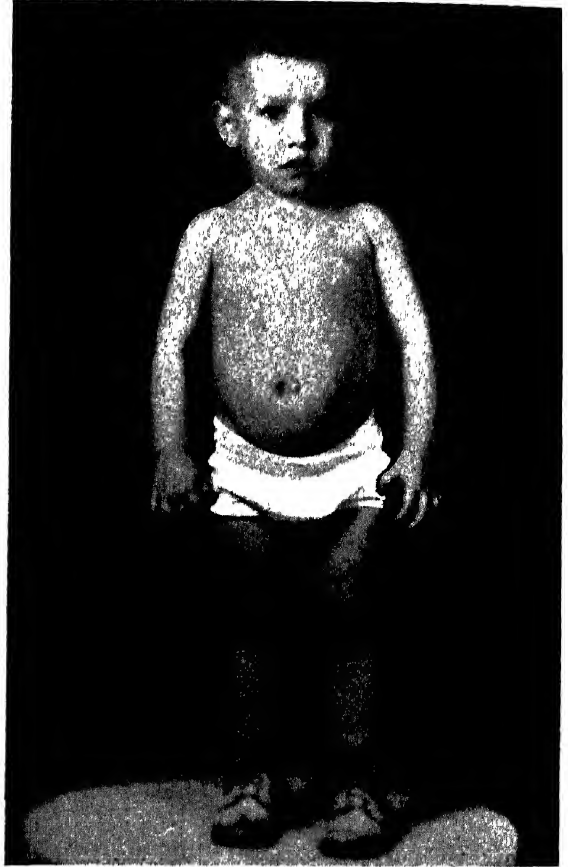


Fig. 3—Showing the patient two years after operation. (Courtesy of H. S. Munroe, Jr.)

tion will determine the site of the tumor, while roentgenography will show the cyst to be part of the liver. One of the most important signs is that pointed out by Hoffmann; with large cysts or tumors of the liver, the colon is pushed downward and to the left of the abdomen, while in the case of neoplasm or other enlargements of the kidneys, the colon overlies the tumor. This point may be easily demonstrated by barium enema. In the case of all large pedunculated cysts of the

liver, downward displacement is limited by anchorage to the liver but a considerable degree of lateral motion is often obtained. Induced pneumoperitoneum followed by roentgenologic examination has proved of little help. Peritoneoscopy

*tirpation along with drainage and marsupialization*, or just *drainage along with marsupialization* have produced satisfactory end results in most cases. In some instances in which external drainage has been done a status



Fig. 4—*A*, Illustration of size and location of liver tumor. *B*, Drawing which demonstrates methods of isolating tumor preliminary to excision. (C. D. Benson and G. C. Penberthy: Surgery.)

may be an aid in diagnosis. Liver function tests, as a rule, show little deviation from normal.

The only treatment for solitary cysts of the liver is *surgical intervention*. **Complete extirpation** of the cyst should be undertaken if conditions permit. Frequently this is impossible. **Partial ex-**

has remained for a few months to years.

A 9-month-old child with a solitary non-parasitic cyst of the liver is presented. The cyst wall was extremely thick and a large portion of the cyst was intrahepatic. There was no tendency toward a cystic collapse following aspiration of the contents. Due to thickness and rigidity of the wall of the cyst, the patient's general condition, and the improbable chance of

adequate closure, radical removal of this cyst was not attempted. A portion of the wall was excised for pathological study, and the cyst wall was marsupialized to the peritoneum and the posterior rectus sheath. The end result was satisfactory, a complete cure being anticipated.

cal liver. Adjacent smaller cysts merged into the larger ones. The pressure upon the surrounding liver tissue may result in atrophy. The latter has been commonly observed in cirrhosis or other

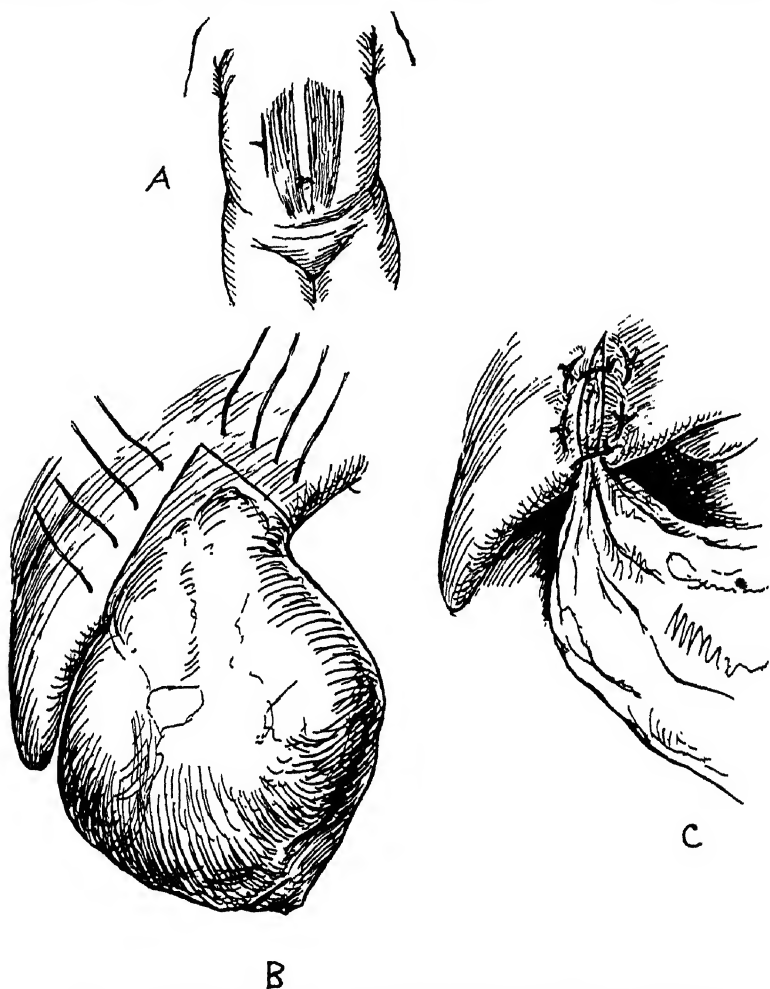


Fig. 5—Type of incision. *B*, Illustration of method of inserting sutures and the line of excision of tumor. *C*, Omentum placed in liver wound and fixation of omentum with chronic sutures. (C. D. Benson and G. C. Penberthy: *Surgery*.)

It was felt that this was a case of hamartoma. Most solitary cysts of the liver should be classified as hamartomatous unless pathological examination reveals evidence of carcinomatous character of a papillary cystadenoma. True blastomatous nature of liver cyst is felt questionable. The enlargement may be explained by gradual increase of fluid with proportionate increase in the number of lining epithelial cells with a physiologi-

scars of the liver tissue. It is associated with proliferation of the bile ducts. Proliferating bile ducts, in the wall of liver cysts, do not necessarily indicate true blastomatous nature of the cyst. The cyst may communicate with a large lumen which can be interpreted as a result rather than the origin of the cyst.

Benson and Penberthy<sup>14</sup> report a successful and complete excision of a primary encapsulated tumor (hamartoma)

of the liver in an infant of seven months. Through a laparotomy incision, the tumor was isolated. Through-and-through chromic catgut sutures were placed in the liver substance approximately 0.5 cm. away from the borders of the tumor. The tumor was excised with a cautery knife as illustrated in Fig. 4b. Hemostasis was accomplished by touching all points of the liver with a Bovie coagulation blade. The free edge of the great omentum was tucked into the operative defect of the liver and anchored in place by chromic catgut sutures. At this point the patient was treated for shock by 100 cc. of *blood*. The abdomen was closed and recovery followed.

Recognition of tumors of the liver in patients is important. All such patients deserve exploratory laparotomies because, in spite of the fact tumors invariably carry a poor prognosis, occasionally a benign tumor such as the one described will occur. Complete surgical removal will offer a good prognosis. Hamartoma of the liver can be considered benign for the following reasons: (1) It is well encapsulated and has embryonal characteristics; (2) it shows no tendency to invade the neighboring tissue; (3) on microscopic examination, no mitotic figures are found; (4) metastases do not occur, and (5) symptoms arise only when the progressive growth of the tumor causes subsequent displacement of neighboring structures.

### Carcinoma of the Liver

Platou and Hill<sup>15</sup> describe two cases of primary carcinoma of the liver in infants aged two and three and one-half months, respectively. Histologically, the tumor tissue consisted of closely packed cords, tubes, and alveoli made up of cells surprisingly similar to those of the normal liver. Adjacent liver tissue showed pressure atrophy and necrosis.

The differential diagnosis in infancy involves:

- a. Other tumors:
  - 1. Metastatic in origin:
    - (a) Tumor of the kidneys (Wilm's).
    - (b) Adrenal embryoma for adenocarcinoma.
    - (c) Cysts (amebic hydatid).
  - 2. Primary in liver:
    - (a) Hemangioma.
    - (b) Cysts.
    - (c) Sarcoma.
- b. Congenital syphilis of the liver.
- c. Inflammatory hepatomegaly:
  - 1. Diffuse.
  - 2. Localized—abscess, single, or multiple.
- d. Leukemic infiltration.

With the hepatomegaly, evidences of dyspepsia appear early, but icterus and ascites are surprisingly uncommon in children. The presence of a primary tumor in the liver may be suspected only because of associated pressure symptoms. Enlargement of the liver upward, encroaching on the thoracic cavity, has been considered a valuable diagnostic sign. The onset of symptoms may be sudden or insidious, and the course is usually complete in less than four months. Surgical intervention in children has been attempted in only a few cases; four successful results have been reported. The youngest of these patients was 10½ months old. Early exploration and biopsy, followed by excision in proven cases, offers the only hope of cure.

Steiner<sup>16</sup> outlines a theory for the chemical causation of cancer, and points out its possible relationship to the theory of chronic irritation.

Twelve sarcomas were induced in 37 mice at the site of subcutaneous injections of the nonsaponifiable lipid fraction extracted from pooled noncancerous livers of persons who died from cancer. The injection time was 182 days and the percentage yield was 32.4 per cent.

An extract similarly prepared from the livers of noncancer bearing persons has less carcinogenic activity, with an injection time of 12 months and a percentage yield of 14.3 per cent. Five sarcomas were induced in 35 mice. Neither of these two extracts induced tumors in rabbits. A benzene extract of cancerous livers failed to induce tumors at the site of injection.

The chemical nature of the carcinogen found in the liver is unknown, other than that it belongs to the general group of the nonsaponifiable lipids. Its origin, whether exogenous or endogenous, likewise has not been determined. An exogenous origin is not excluded because of its presence in the liver. These points are now under investigation.

### Amebic Disease

Ochsner and DeBailey<sup>17</sup> state that 287 patients with liver abscess were seen within a 14-year period. Of this number, 181 (63 per cent) were amebic and 106 (37 per cent) were not amebic. In addition to studying these cases, the authors reviewed the literature (SEE: *Tropical Medicine*).

The relative frequency and increasing significance of amebiasis is pointed out. A fallacious impression still exists that amebiasis is an acute disease usually contracted in the tropics and manifested principally by dysentery or liver abscess. The authors quote Craig, who is of the opinion that the average incidence of amebiasis in the United States is as high as 20 per cent rather than the accepted figure of 5 or 10 per cent. Thus it would seem that about twenty million to twenty-five million people in the United States are infected with the parasite. The surgical significance of this appallingly high incidence lies in the potential development of hepatic infections. Approximately 4 or 5 per cent of the individuals

with intestinal amebiasis develop hepatic complications; thus, approximately one million people in the United States suffer from hepatic complications of amebiasis.

In a collective series of 5211 fatal cases of amebiasis, 36 per cent were found to have hepatic abscess. The lowest incidence in this group was 7.6 per cent and the highest was 84.4 per cent. The incidence of hepatic abscess in all cases of intestinal amebiasis varies, according to the different reports, and seems to depend upon whether the cases were ambulatory or not. In collected cases of 9696 cases of clinical amebiasis, including the authors', there were 472 cases of amebic abscess of the liver, an incidence of 4.86 per cent. The incidence was 17.4 per cent in the 160 cases among 1333 of amebic dysentery of Charity Hospital. A study of the cases at various time periods indicates that the incidence of amebiasis has continued to increase but the incidence of complicating hepatic abscess has been decreasing during the last four years, although it was increasing up to that time. This suggests that intestinal amebiasis is being recognized earlier and treated more effectively than in recent years. Statistical studies on the incidence of amebic hepatitis and hepatic abscess, according to localities of the country and hospital admissions, are confusing and definite conclusions cannot be drawn from a review of the reported cases.

The condition is much more common in males than in females. Amebic hepatitis and hepatic abscess occur principally during adult life and few cases have been observed in individuals less than 20 or more than 50 years of age. In the reported series of 181 cases, the youngest patient was six years old and the oldest 70. The average age was about 40. The patients were approximately a decade

older than the tropical cases reported. In the tropics the natives suffer less than white people. The comparative mildness of amebic symptoms among natives in the tropics is due largely to an immunity developed from childhood. In the series studied, of 160 cases 87 or 54.4 per cent were white and 73 or 45.5 per cent were colored. Other factors, such as alcoholism, traumatism, exposure, improper diet, and lowered resistance have been considered to have some predisposing influence upon the development of the amebic hepatitis and hepatic abscess. Of these, excessive indulgence in alcohol is believed by most authorities to be the most important. In fact, some have cited the more abstemious habits of females as a significant factor in the comparative freedom from this complication. The significance of seasonal influence upon the development of amebic hepatic abscess is questionable.

**Pathogenesis** — The three possible routes by which ameba may gain access to the liver are: (1) By direct extension through the bowel wall, peritoneal cavity, and the capsule of the liver; (2) by the lymphatic route; (3) through the portal vein. Most authorities agree that the amebae enter the liver through the portal vein from a primary focus in the intestines.

In the development of amebic hepatitis and hepatic abscess two factors which played prominent rôles are: (1) Production by the ameba of intrahepatic portal thrombosis and infarction; (2) the cytolytic activity of the ameba. Amebae lodge in the smaller portal radicals, producing thrombosis with typical infarction and consequent focal necrosis. These appear characteristically in the portal vessels, and extend peripherally towards the capsule, thus paving the way for the cytolytic activity of the ameba to produce

hepatitis and destruction of the involved liver parenchyma. In many instances this early process of amebic hepatitis healed by connective tissue replacement. According to this concept it is obvious that in the early phase of an amebic hepatitis a balance exists between the regression towards healing by scar tissue replacements and progression towards suppuration and abscess formation.

The amebae are found characteristically in the zone of necrotic tissue adjacent to the outer dense fibrotic abscess wall. They can be demonstrated with greatest frequency in the earlier stages of amebic hepatitis or in the marked necrotic tissue of early abscesses; more rarely, they are found in the older abscesses with a thick fibrotic capsule. Probably this accounts for the fact that amebae are so difficult to find in the contents of large amebic abscesses, especially when first opened, although several days later they may be found in the pus. This may be explained by the fact that amebae require oxygen and, after the abscess is opened and exposed to air, the amebae rapidly appear in the drainage material. While pathogenic organisms are associated with amebic abscesses, they are secondary invaders rather than predisposing factors to the development of an amebic abscess. The organisms most commonly found in the secondarily infected hepatic abscesses are streptococci and staphylococci. However, other forms, such as enterococci, *Bacillus coli*, and pneumococci, have been reported.

**Pathology**—The gross appearance of the liver in amebic abscess varies depending upon the location, degree, and stage of involvement. Usually the liver is enlarged, although if the abscesses are small and deeply situated, it may be fairly normal on external appearance. On the other hand, localized peritonitis is usu-



ally present on the surface in those cases in which the abscess lies near the capsule. Adhesions to the diaphragm are present in those peripherally located abscesses in the dome of the liver. On section the abscesses become easily visible and the surrounding parenchyma presents evidence of fatty degeneration and venous congestion.

The abscesses have been divided into three types: (1) Small, which are acute; (2) the larger abscesses with partially fibrinous walls; (3) the chronic, with hard, dense, fibrous shells. In the earlier stages of the noninfected amebic abscess, the material has a viscid, glairy, semi-transparent appearance. Later the contents become less viscid and, due to the mixture of blood, assume a yellowish-red or chocolate-brown color. *This characteristic appearance of the material contained in the abscess has been variously described as resembling liver scrapings, crushed strawberries, wine dregs, anchovy sauce, and chocolate sauce. This material is so characteristic of an amebic abscess that its presence justifies a positive diagnosis even when the amebae are not demonstrable.* When secondary infection occurs, the contents are purulent and develop a greenish or grayish-yellow creamy character.

Likewise, the abscess wall is dependent upon the stage of abscess formation. Early it may be scarcely visible, whereas in the later stages a dense, well-defined fibrous tissue capsule, varying in thickness, is conspicuously present. This thick wall is due to the fact that connective tissue of the liver offers marked resistance to cytolysis and the invasion of tissue with this parasite stimulates connective tissue formation. The microscopic appearance of the abscess also varies according to the stage of the process. Early, one sees cytolized and de-

generated liver cells, red cells, and a few leukocytes and fibroblasts, occasional amebae surrounded by zone capillary congestion. As the lesion advances to the true abscess formation, a well-defined wall of connective tissue appears surrounding the cavity containing granular necrotic liver tissue, erythrocytes, lymphocytes, and a few polymorphonuclear leukocytes. In the periphery, amebae can frequently be observed invading surrounding liver parenchyma.

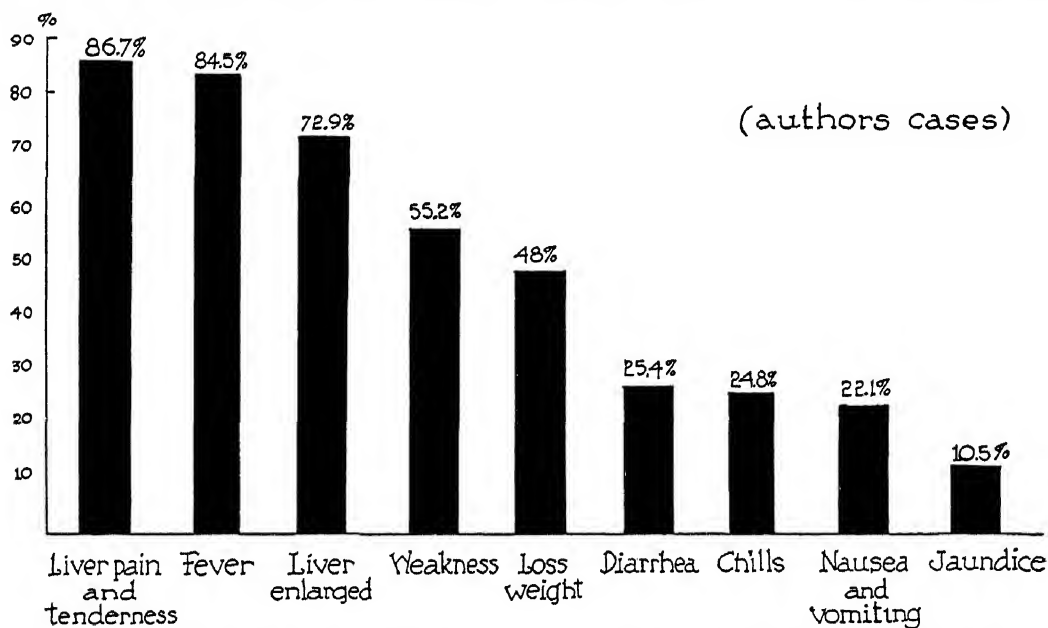
The location and number of hepatic abscesses may be variable; however, they are usually single and occur in the right lobe near the dome of the liver or on the inferior surface near the hepatic flexure of the colon. The predominance of the right lobe involvement may be explained on the basis of two currents of blood in the portal vein, one from the superior mesenteric vein, which goes to the right lobe, and one from the inferior mesenteric and splenic veins, which goes to the left lobe of the liver. It has been shown that amebic lesions are encountered most frequently in the cecum and ascending colon. On the basis of the two currents of blood in the portal vein, this area drains into the right lobe of the liver; consequently, there is greater likelihood of amebic localization in this lobe.

**Clinical Manifestations**—The onset of amebic hepatitis or hepatic abscess varies considerably and may be acute, subacute, or insidious, depending upon a number of factors, such as the virulence of the infection, the resistance of the host, and other previously mentioned factors. Complications may also develop during or immediately following the stage of acute intestinal amebiasis, during active or quiet periods of chronic intestinal amebiasis, in healthy carriers, or in patients who have never had dysenteric manifestations. The period elapsing be-

tween the dysenteric manifestation and the onset of liver involvement may vary considerably, although it is usually from one to three months. In some of the cases in this series the period extended from six to eight years. The importance of recognizing the early development of amebic hepatitis has been repeatedly emphasized. During this early period, or presuppurative stage, there is invasion of the liver by amebae, but true abscesses have not yet occurred. Appropriate therapy at this stage may prevent abscess

153 of 181 cases (or 84.5 per cent). The order or frequency of other symptoms may be well seen from Graph I.

The earliest and *most constantly encountered local manifestation* of amebic hepatitis is *pain and tenderness in the region of the liver*. This is present in from 75 to 100 per cent of the cases reported in the literature and in the series reported there was an incidence of 86.7 per cent (Graph I). Pain varying from a dull aching discomfort to sharp pain, usually located over the liver, was fre-



Graph I—Relative incidence of various clinical manifestations in amebic hepatitis and hepatic abscess, based upon analysis of 181 cases of authors. (A. Ochsner and M. DeBakey: Surgery.)

formation. In the author's series of 181 cases, 68 (or 37.6 per cent) were acute and 113 (or 62.3 per cent) were chronic. In the acute group the shortest duration was one day and the average was from ten days to two weeks. In the chronic group the longest duration was three years and the average from three to six months.

The clinical manifestations of amebic hepatitis and hepatic abscess may be divided into two groups: (1) Systemic; (2) local. Fever is the most frequent systemic manifestation. It was present in

quently noted. Radiation to the shoulder, usually to the right, was a prominent complaint and may be explained on the basis of diaphragmatic irritation. In the series reported it was recorded in 16.6 per cent of the cases. The *next most constant local manifestation is enlargement of the liver*. The incidence of this has varied from 64 to 100 per cent. In the author's series of 181 cases the liver was clinically enlarged in 72.9 per cent. Manifestations of liver enlargement are sometimes apparent by widening of the lower right intercostal spaces with some

restriction of respiratory movement on this side and dilatation of the superficial vessels. Usually the liver margin can be palpated below the right costal arc anteriorly and, on percussion, liver dullness will be found to extend higher than normal, especially in the mid- or posterior axillary line. Frequently tenderness and some rigidity of the abdominal muscles in the upper right quadrant can be elicited. Associated diaphragmatic pleural and basal lung changes on the right side are not uncommon. This is manifested by localized pain, especially on deep inspiration; a hacking, nonproductive cough; dullness; diminished breath sounds; crepitant râles, and a friction rub. In some cases there may be signs of fluid in the pleural cavity. Such signs vary according to the extent of hepatic involvement.

**Laboratory Finding**—The most informative laboratory procedures in amebic hepatitis and hepatic abscess are certain blood studies, stool examinations, and roentgenography. A moderate leukocytosis as compared with a marked leukocytosis in the pyogenic form of liver abscess is significant. The degree of leukocytosis varies from 16,000 in the acute form to 13,000 in the chronic form. A high leukocytosis indicates multiple abscesses and a bad prognosis. It may also indicate secondary invasion of pyogenic organisms. In the pyogenic abscesses, the average leukocytosis has been found to be around 26,000 as contrasted with 16,000 in the amebic. A complement fixation test may be used; however, the difficulty in obtaining a potent antigen has hindered the routine use of this test. The detection of ameba in the stool varies with the technic employed, the experience of the examiner, and frequent repetition of the tests. In the reported series, this test was performed in 107 cases, the ameba being found in 39

(or 36.4 per cent). Roentgenography is undoubtedly one of the most important and dependable diagnostic laboratory procedures in amebic hepatic abscess. Fluoroscopic examination of the patient in the upright position shows the elevation and immobility of the diaphragm. The presence of lung reaction is diagnostic because these abscesses occur on the convex surface of the liver in close relation to the diaphragm. A positive diagnosis may be made in from 80 to 88 per cent of the cases by roentgenographic studies. Aspiration of the pus followed by injection of an iodized oil has been suggested as a means of roentgenologic study. In the author's opinion, this should not be routinely employed. Hepatography by the intravenous administration of thorium dioxide has also been advocated. The abscess appears as a negative shadow. The danger of radioactive substance is not sufficiently understood to warrant routine use of this procedure.

**Diagnosis**—Amebic hepatitis should always be considered in a patient presenting a low grade daily remittent or intermittent fever, pain and tenderness over the liver area, moderate leukocytosis without a concomitant proportionate increase in polymorphonuclear leukocytes, and *E. histolytica* in the stool. Such a clinical picture during or shortly after an attack of amebic dysentery strongly indicates the presence of amebic hepatitis. The absence of intestinal manifestation does not rule out the possibility of amebic hepatitis.

While there is some variation in the clinical manifestations of amebic hepatic abscess depending upon the stage of the abscess, persistent hepatomegaly, pain, and tenderness over the hepatic area with occasional radiation to the shoulder, and a daily remittent or intermittent fever of moderate degree are fairly constant manifestations. The presence of these symp-

toms and signs should always suggest the possibility of amebic hepatic abscess. Anorexia, loss of weight and strength, nausea and vomiting, profuse perspiration, and disturbed slumber are less frequently observed, but their presence lends further to support of the diagnosis. The presence of an antecedent dysentery is confirmatory evidence, but its absence does not rule out hepatic abscess. Between one-third and one-half of the patients gave no history of previous dysentery. Moderate leukocytosis, characteristic fluoroscopic and roentgenologic findings are confirmatory evidence.

A positive diagnosis depends upon the demonstration of the characteristic chocolate-sauce pus on aspiration. The possible dangers of aspiration are hemorrhage and extension of infection. These hazards may be avoided by *pre-aspiration emetine therapy*, the type of needle employed, the technic of aspiration, and the performance of the procedure in the operating room under absolute aseptic precautions. Emetine hydrochloride administered in doses of 0.065 Gm. (1 grain) daily two to four days prior to aspiration. A needle not longer than 10 cm. and not greater than 2 mm. of the short level type is preferable.

**Prognosis**—In addition to the relative number and virulence of the parasites and the resistance of the host, the most important factors are: (1) The multiplicity of lesions in the liver; (2) presence or absence of complications; (3) the presence or absence of secondary infection; (4) type of therapy employed. Multiple abscesses increase the gravity of the condition. The mortality of 16 patients with multiple abscesses was 100 per cent, whereas in 124 cases with single abscesses it was only 10.5 per cent. The presence of secondary infection greatly increases the risk. In the series reported, the mortality in 39 cases with

complications was 41 per cent, in contrast with 141 cases without complications in which the mortality was 8.5 per cent. Thus, while the majority of amebic abscesses are sterile when secondary infection occurs, the abscess can no longer be considered on the same basis as a simple amebic abscess. It is difficult if not impossible to perform open drainage of the abscess and prevent secondary infection. Therefore, the best treatment is closed aspiration of the abscess. A mortality in 24 cases with transpleural drainage was 33.3 per cent and 23 cases with transperitoneal drainage 30.4 per cent. Whereas in 15 cases drained by the extraserous route, the mortality was only 6.6 per cent. Nineteen cases were drained by simple incision over the abscess with a mortality of 10.5 per cent. Since these abscesses had become attached to the parietes and thus sealed off from the serous cavities, drainage in these cases must also be considered extraserous. Accordingly, the mortality in those having extraserous drainage would only be 8.8 per cent as contrasted with 31.5 per cent in those drained transserously.

**Treatment**—The treatment of amebic hepatic infection is entirely *surgical*, although it should be realized that this may consist of either conservative or radical measures, depending upon certain developmental factors. Early recognition of amebic hepatitis and institution of conservative measures may prevent the formation of an actual abscess. Early abscesses may respond to conservative measures. Conservative therapy means the administration of a specific drug, *emetine hydrochloride*, with or without aspiration, depending upon the indications for the latter. The drug is administered subcutaneously as emetine hydrochloride in daily doses of 0.065 Gm. (1 gr.) until 0.39 or 0.65 Gm. (6 or 10 gr.) have been given. Due to the

toxicity of excessive dosage and its cumulative action, considerable care should be exercised in its use. Degenerative changes in cardiac musculature follow prolonged use. The clinical manifestation of toxicity consists of severe diarrhea, nausea and vomiting, profound prostration, cardiac arrhythmia and failure, muscular pains, and weakness, especially of the extremities. Other amebicides, such as *acetarsone*, *carbarsone*, *treparsol*, *chiniofon* (*anayodin* and *yatren*), *vioform*, and *diodoquin*, which are safer and more efficient in the treatment of intestinal amebiasis are not considered desirable in the treatment of amebic hepatitis or hepatic abscess because they are not as effective in these conditions as emetine. However, immediately following the completion of therapy for the amebic hepatic condition, the patient should be given a course of therapy for intestinal amebiasis with one of these drugs.

**Aspiration** is the procedure of choice when evacuation of the abscess becomes necessary. In these cases, preliminary administration of emetine is important. It is necessary to maintain utmost care concerning sterility and prevent open operation and drainage if possible. The administration of emetine should be continued after closed drainage of the abscess until 0.39 to 0.65 (6 to 10 gr.) have been given. It is undesirable to introduce any substance into the abscess cavity.

**Open drainage** is necessary in the secondary infected cases. The use of *sulfonamides* may prevent the use of open drainage in infected abscesses, thus lowering the mortality. The anterior or posterior extraserous approach is the best in open operation and if open drainage is required. The anterior approach is by an incision parallel to the costal margin traversing the oblique muscles

and transversalis fascia, and approaching the abscess extraperitoneally by carefully mobilizing the parietal peritoneum from the lower surface of the diaphragm. In the posterior abscesses, the retroperitoneal approach is the most rational. This consists briefly of a subperiosteal resection of the twelfth rib and entering the retroperitoneal space through a transverse incision made at the level of the spinus process of the first lumbar vertebra in the bed of the resected rib. The liver abscess is approached extraserously by carefully mobilizing the parietal peritoneum on the undersurface of the diaphragm. The comparatively low mortality of 6.6 per cent in 15 cases is convincing evidence of its value. The secondarily infected amebic abscess which is pointing should be opened over the point of greatest localization. Failure to treat the intestinal infection properly accounts for recurrent abscesses.

**Complications** — Complications of amebic hepatic abscesses consist essentially of secondary infection with pyogenic organisms, direct extension or rupture of the abscess into one of the adjacent viscera or serous cavities, and thrombosis or embolism. Their occurrence usually signifies negligence or procrastination on the part of the patient but occasionally reflects the physician's mismanagement. Thus, the development of peritonitis or empyema following that type of open drainage which does not completely avoid contamination of these virgin serous surfaces is obviously not due to the patient's disregard but is an example of the latter possibility. Moreover, lack of recognition of the condition sufficiently early undoubtedly accounts for the development of some of the complications. Pleuropulmonary involvement is the most frequent complication. In the majority of cases this is the result of rupture or direct extension of the liver

abscess through the diaphragm. In a collected series of 2490 cases of hepatic abscess, pleural complications occurred in 7.5 per cent and pulmonary complications in 8.3 per cent. In 181 cases reported, pleural complications occurred

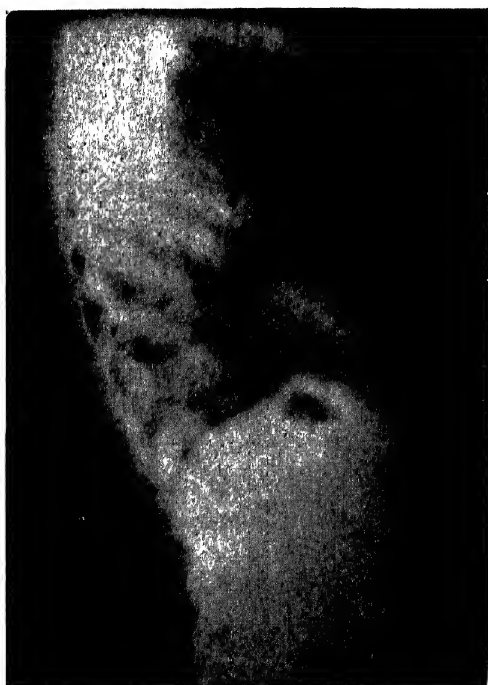


Fig. 6—Lateral roentgenogram of the chest of the patient taken after diagnostic thoracentesis which revealed chocolate sauce pus. The fluid level may be clearly observed in the right pleural cavity. (A. Ochsner and M. DeBakey : Surgery.)

in 5 per cent and pulmonary in 9.4 per cent, giving a total incidence of 14.4 per cent. Of the 26 cases with pleuropulmonary involvement, eight developed bronchohepatic fistula, nine empyema, and nine pulmonary abscess. Extension into the peritoneal cavity is the next most frequent complication of amebic hepatic abscess. There were 13 cases in the 181 cases studied of an incidence of 17.2 per cent. Localized or generalized peritonitis will follow rupture into the peritoneal cavity. Thus, the clinical manifestations will vary, depending upon the mode of development and the presence or absence of general or localized peritonitis. The

presence of a localized or generalized peritonitis also influences the therapy; although emetine should be administered in all cases, in the former aspiration should be done first and if secondary infection is demonstrated, immediate local drainage should be instituted. This is necessary in the majority of cases and was done for three of the 13 in this series. In the remaining cases the patients died soon after the onset of generalized peritonitis.

Occasionally an amebic abscess will rupture into the pericardial cavity. This

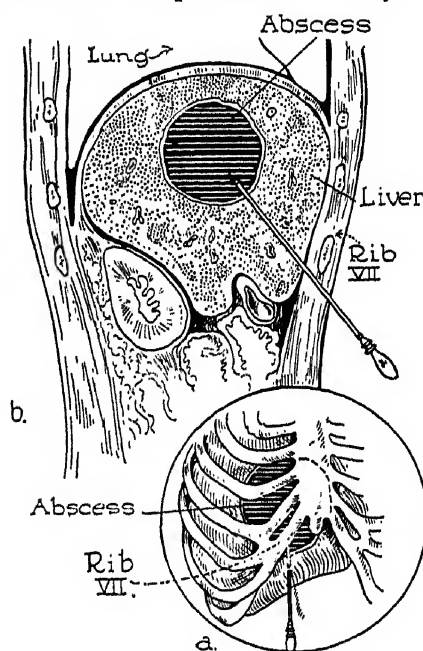


Fig. 7—Technic of aspiration of amebic hepatic abscess located in anterior portion of liver: *a*, The needle is inserted just below the anterior costal margin about 4 to 6 cm. lateral to the midline. *b*, Diagrammatic representation of sagittal section at level of cutaneous puncture showing needle directed superiorly and posteriorly into abscess cavity. (A. Ochsner and M. DeBakey : Surgery.)

complication occurs in less than 2 per cent of the cases. The rarer complications of amebic hepatic abscess are perforation into the gastrointestinal tract, supensory ligament, through the abdominal wall, into the biliary tract, into the portal vein, and inferior vena cava. Perforation of or drainage of the abscess

through the abdominal wall may be followed by cutaneous amebiasis which requires radical excision and the use of emetine in the treatment. Even rarer complications are cerebral abscess, extension of the amebic hepatic abscess into the spleen and kidneys.

Case histories illustrating characteristic satisfactory response to various forms of therapy are presented.

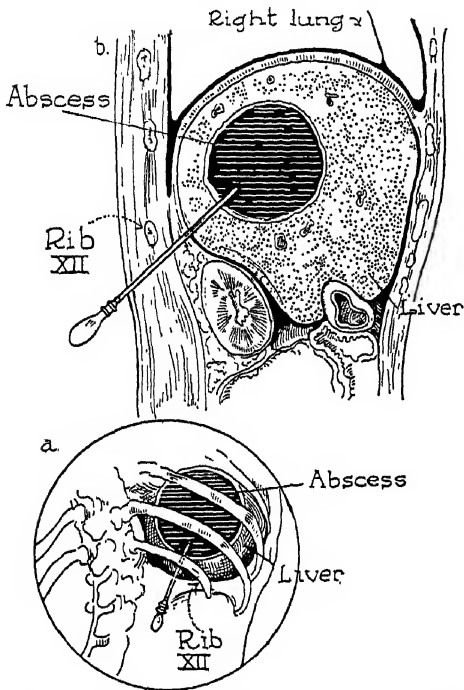


Fig. 8—Technic of aspiration of amebic hepatic abscess located in posterior portion of liver. *a*, The needle is inserted in the right lumbar costal angle. *b*, Diagrammatic representation of sagittal section at level of cutaneous puncture showing needle directed superiorly and anteriorly into abscess cavity. (A. Och-sner and M. DeBakey: Surgery.)

Brea *et al.*<sup>18</sup> report a case of hepatopulmonary amebiasis in a 25-year-old man complaining of fever, malaise, hemoptysis, abundant expectoration, and diarrhea. There was tenderness over the right lower chest and dullness in the same region on percussion. The abdominal muscles over the right upper quadrant were rigid; other important symptoms were tachycardia, and chocolate-colored sputum. No parasites could be

detected in the sputum or the feces. X-ray examinations revealed an elevation and deformity of the right dome of the diaphragm and an infiltration of the lower portion of the right lung, which formed a dense shadow with supernatant fluid and air. Aspiration of the right lower lung disclosed the presence of dysenteric entameba. A transparietal injection of the lipiodol demonstrated a communication between the liver and the pulmonary shadow. Prompt recovery followed the use of *emetine* and *yatren*.

The authors state that in spite of an endemic amebiasis in Argentina, its pulmonary location is rare, and a communication between a pulmonary abscess and the liver is very unusual. During the infiltrating or pneumonic period, the symptoms of an amebic abscess are non-specific, but in the course of the following period of suppuration or liquefaction, bile may appear in the sputum if communication with the liver is wide. Blood is responsible for the characteristic chocolate-like appearance of the sputum.

Berne<sup>19</sup> studied 74 cases of amebic abscess and points out certain diagnostic and therapeutic considerations shown by the study. While amebic infection of the colon always antedates the liver lesion, many cases have no symptoms of colitis. Thirty of the cases gave a history of diarrhea, 44 fail to recall diarrhea, while six complained of constipation. Gross colon lesions were present in 14 of the 24 cases in which postmortem examinations were made. In five of these there had been no diarrhea. The surgeon must therefore commonly diagnose a complication, amebic hepatic abscess, in the absence of any signs of primary disease. Whether or not diarrhea is present, the stool usually contains cysts. In 55 cases in which stool examination was performed, 40 were positive. Saline cathartics are helpful in raising the incidence



of positive stools. Only five of the cases occurred in women. None of the cases occurred in patients under 20 years of age. Alcohol could not be shown to be a predisposing factor. There seems to be a relationship between trauma and the development of amebic abscess. In three instances, the patient was entirely well at the time of a considerable trauma to the liver region, and immediately developed symptoms, subsequently proved to be due to amebic abscess. It is suggested

liver. The authors point out four syndromes: an acute costal margin syndrome, a chronic costal margin syndrome, an acute pulmonary, and a chronic pulmonary syndrome. Each of the four involves a separate field of differential diagnosis. The chronic syndrome at the costal margin includes cases which may be misdiagnosed as malignancy of the liver, stomach, gallbladder, or colon; sclerosis; amyloid disease; echinococcus cysts; pancreatic cysts, or *hepar lobatum*.

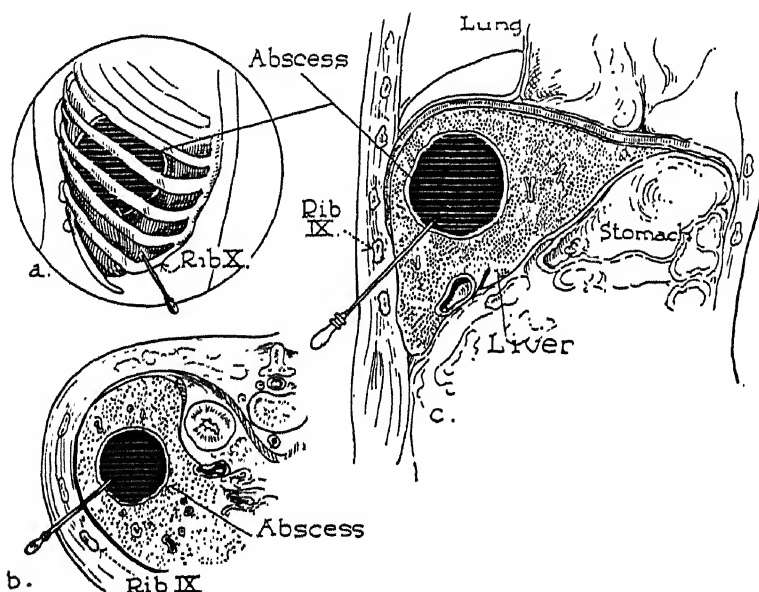


Fig. 9.—Technic of aspiration of amebic hepatic abscess located near dome of liver. *a*, The needle is inserted through the ninth or tenth intercostal space in the anterior axillary line. *b*, Composite diagrammatic representation of horizontal section through liver abscess and cutaneous puncture site showing posterior and medial direction of needle. *c*, Diagrammatic representation of sagittal section at level of cutaneous puncture showing superior direction of needle into abscess cavity. (A. Ochsner and M. DeBakey: Surgery.)

that amebic infestation of the liver is compatible with an absence of any significant lesion, because trauma could only operate by activation of a latent infection. Instead of regularly being chronic, the process was an acute severe disease in 58 per cent of the cases. The second important feature was an absence of abdominal features in 33 per cent of the cases instead of the lesion being in the upper right quadrant. The clinical phenomena were pulmonary, because the abscess was located near the dome of the

The acute syndrome at the costal margin is more frequently misdiagnosed as acute cholecystitis, penetrating or perforated duodenal ulcer, or an abscess complicating either peptic ulcer or cholecystitis. The chronic pulmonary syndrome closely resembles cancer of the lower lobe when chronic pneumonitis exists without pleural effusion, whereas if effusion exists tuberculosis or cancer are usually considered responsible. In the acute pulmonary form basal pneumonia is repeatedly diagnosed and empyema is added when

effusion occurs, or an acute pleurisy with effusion is considered to be present. In such cases a bronchial fistula may fortunately occur, and the appearance of anchovy sauce sputum develops a correct diagnosis. If the left lobe of the liver be involved by the amebic abscess again the process may be acute or chronic, and the phenomena occur in the epigastrium rather than in the left costal margin, and if transphrenic effects appear they are likely to be pericardial. Hepatomegaly is a constant feature, often detectable in the bedside examination, and usually demonstrable by roentgenologic study. Even with dome abscesses, there is often downward enlargement. In the very chronic cases an abscess may point and produce a mass which can be recognized to be arising from the liver. One of the patients had such a mass for 20 years and the condition simulated very closely echinococcus cysts of the liver.

As far as the treatment was concerned the cases were divided into three groups: those apparently cured with *emetine* only; those requiring *aspiration* in addition to emetine, and those treated *urgically* with or without emetine. Nineteen of the patients were treated with emetine alone, with complete recovery in all cases. The largest total dose of emetine was 1 Gm. (16 grains), the average 0.613 Gm. (9.5 grains). The drug was administered intravenously in ten and intramuscularly in nine. Four cases with negative aspirations were included in this series. There were also three cases of bronchohepatic fistula.

There were 18 cases treated by emetine and aspiration without a death. The amount of emetine given varied from 0.26 to 1.555 Gm. (4 to 24 grains); the injections being intravenous in 15 and intramuscular in three. Three required three aspirations and the largest amount aspirated at any one time was 2200 cc.,

the lowest 45 cc. Two cases are included in which at the time of laparotomy an abscess was discovered, the abscess was aspirated, the abdomen was closed without drainage. The question of multiple abscesses requires consideration. In seven of the 24 autopsies multiple abscesses were present. In none of the treated cases was more than one recognized.

The surgically treated group consists of 26 cases, 14 adequately treated with emetine. The mortality was 53 per cent. This group is in no way comparable with the previous group. In four there were acute intraperitoneal ruptures, the patients were operated upon for duodenal perforations, and three survived. If such an abscess is small and has emptied itself, drainage is of no value, while if it is large and still leaking, a short period of drainage is indicated. Two cases of rib resection were done for secondary infection of the pleura. Of these two, one lived, the other died with empyema.

In concluding, the author points out that the disease is in no way confined to the tropics; the liver lesion is not, in the usual sense, an abscess, and amebic dysentery actually describes only the severe form of amebic colitis. The resultant constricted conception has served as a basis for innumerable diagnostic failures. It must be realized that amebiasis is endemic in temperate climate and that amebic hepatic abscess is a special type of liver necrosis for which there is specific chemotherapy. There should be a more frequent suspicion of the presence of the disease and improvement in the therapy applied.

Meredith *et al.*<sup>20</sup> made the diagnosis of solitary hepatic abscess by hepatosplenography with thorium dioxide solution as a contrast medium. The location of the lesion served as a guide for aspiration. They felt that the method was

indicated for the diagnosis of the hepatic abscess. The possible potential danger, from the radio activity of thorium that remains in the body indefinitely, has not been supported by clinical experience. They pointed out that microscopic study of the tissue from 65 patients injected by Yater and Whitmore with thorium dioxide solution for hepatosplenography revealed no evidence of injury to the tissue or any cellular reaction ascribable to the presence of thorium dioxide. Furthermore, a comprehensive survey of 286 cases covering 10 years of experience in hepatosplenography has revealed no evidence of immediate or remote ill effects in patients of Yater and Coe. The remarkable point concerning this series of patients was the fact that they had lived longer than was anticipated and have been in moderately good health.

### The Hepatic Factor in Burns

In a series of 1243 burns treated for a period of  $6\frac{1}{2}$  years, there was a mortality of 217 or 17.45 per cent recorded by Boyce.<sup>21</sup> In 78 patients, over 50 per cent of the body surface was involved; in 14 of the patients who died, only 15 per cent, and in nine, only 10 per cent of the body surface was involved. In many of the fatal cases the burns were of the first and second degree. The persons at the extremes of life are particularly susceptible to deaths from burns. Over 25 per cent of the deaths in this series were in children under five years of age and 20 per cent were in patients over 70 years of age.

Boyce points out that the excessive liver damage, which was present in a vast majority of cases, does not receive sufficient attention. In the clinical picture of toxemia in burned patients, there is a striking resemblance to the clinical picture in such definitely hepatic states as the so-called "liver deaths" or "liver-

kidney" syndrome. The clinical picture pointed out is first a change in the mental state, the patient becoming restless, irritable, apprehensive, then drowsy, comatosed, disoriented and lapsing into delirium. Convulsions are frequent in young children. The temperature rises to 105° F. or higher, pulse and respiration are correspondingly rapid. Vomiting is usually present. Skin and mucous membranes have a cyanotic or grayish tinge, the eyes are sunken, and the pupils are dilated. The most obvious manifestation of hepatic damage is the development of jaundice. In a few cases in which the author performed liver function tests, various degrees of functional impairment were found. Roughly this impairment corresponded to the surface area involved and the depth of the lesion.

The liver lesions vary from extreme changes comparable to those of acute yellow atrophy to serous inflammation, cloudy swelling, or fatty metamorphosis.

Wells *et al.*<sup>22</sup> presents four patients who died as a result of toxemia from burns. The only significant histopathological finding was a hepatitis characterized by central necrosis of the hepatic cells of the liver lobule. The relationship of *tannic acid* to this constant pathological finding was suspected and investigated experimentally. Seventy-seven rats, maintained either on a standard or house diet, were given subcutaneously one or more injections of a 5 or 10 per cent solution of tannic acid. The livers of these animals showed varying degrees of liver necrosis depending upon the amount and frequency of the injection of tannic acid solution. The microscopic findings also included central necrosis, all stages of cellular degeneration, hemorrhage, and leukocytic infiltration. The authors believed that the *toxemia of burns was effected by the use of tannic acid and resulted in liver necrosis.*

The hepatotoxic action of subcutaneous tannic acid injection was confirmed by Forbes and Evans.<sup>23</sup> The pathological picture was one of central necrosis similar to that described by Wells *et al.* In addition they found that substances which give fairly good protection against carbon tetrachloride and chloroform, such as *sulfanilamide* and *xanthine*, afford no protection against tannic acid. For this reason they were of the opinion that the mechanism of the action of tannic acid may be quite different from that of chloroform and carbon tetrachloride. It was felt that it would be necessary to find some other means of protecting the liver besides the high carbohydrate, high protein diets when a patient has been treated by *tannic acid* for a burn.

### Liver Abscess

St. John *et al*<sup>24</sup> point out that abscesses of the liver are usually amebic or pyogenic. The latter may be due to invasion by a variety of organisms, and may follow infection from an area drained by the portal system, spread from contiguous structures, result from trauma by penetration from without or by infection in a hematoma with organisms already present in the liver and blood borne by the hepatic arteries. In many cases, the cause of the infection is not demonstrable. The authors point out the necessity of taking both aerobic and anaerobic cultures in order to demonstrate the exact bacteriological factors involved.

They believe that the case reported by them is the first recorded case of primary solitary hepatic abscess from which a pure culture of an anaerobic nonhemolytic streptococcus was recovered. The portal of entry of the organism was unknown. The symptoms and clinical findings were not constant.

A male patient, aged 19, complained of chills and fever of four weeks' duration. The onset came on two days after playing football in the snow. Anorexia and weight loss were present. The patient also had a mild nonproductive cough. Two weeks after the onset of the illness, there was a slight inconstant pain in the upper right quadrant of the abdomen which caught him when he took a breath. This pain was present two days and then subsided, only to recur six days later. During the latter episode, he complained also of constant pain in his right shoulder, made worse by deep inspiration. The shoulder was not tender, nor was it hot or swollen. There is no history of diarrhea or jaundice, no exposure to enteric disease. He had spent some time in Mexico. He had no unpasteurized milk. There had been a small pustule on the back of the neck several months before the onset of the illness, which subsided without drainage. The laboratory findings were rather complete and inclusive. No improvement followed courses of *sulfathiazole*, *quinine bisulfate*, and *sodium salicylate*.

Physical examination showed a chronically ill young white male; temperature 104° F., pulse 110, respirations 24. A few shotty posterior cervical lymph nodes. Thorax revealed inconstant tenderness over the seventh, eighth, and ninth ribs on the right, and ninth, tenth, and eleventh ribs on the left. This tenderness was more marked on the right side. Examination of the lungs showed a short inconstant friction rub over the seventh and eighth ribs anteriorly on right side. Sometimes, on deep inspiration, the patient showed evidence of pain and the chest expanded less on the left side. Abdominal examination showed upper right quadrant tenderness and spasm. *An interesting observation recorded was the production of pain in the right shoulder with deep inspiration while the patient was supine. The phenomenon could not be reproduced with the patient in a sitting posture.* At operation, 45 days after the onset of the disease, a deeply seated abscess of the right lobe of the liver was found. The right ninth rib was resected directly over the suspected area on the superior surface of the liver. Pleura was incised and immediately sutured to the diaphragm. The diaphragm was then incised, exposing the liver. Two strips of iodoform gauze packing were placed between the diaphragmatic peritoneum and the surface of the liver. The transpleural wound was packed with vaseline gauze. The abdominal incision was closed without drainage. Forty-eight hours later the packing

was removed from the transpleural wound and a small suction trocar was introduced into the soft spot in the liver. At a depth of 3.5 cm. from the surface 60 cc. of yellow-brown pus were encountered. The tract was enlarged with an electrocoagulator without bleeding. A rubber catheter drain was inserted. The postoperative course was uneventful. The abscess drained for 20 to 25 days postoperatively. When seen six months later, the patient had regained his weight, weighing 175 pounds, and had returned to college for two months. Repeated examination of fresh specimens failed to show ameba, giardia, or other parasites. Aerobic culture showed no growth, anaerobic showed a non-hemolytic streptococcus which appeared in subsequent cultures.

The authors felt that pain in the shoulder with deep inspiration in the supine position and its absence in the sitting position may be a contributory sign in the diagnosis of abscess of the liver.

### Hyperthyroidism and the Liver

As a result of clinical and experimental studies, Sealy<sup>25</sup> points out that the liver changes observed in hyperthyroidism are dependent upon a simultaneous factor of infection and hyperthyroidism. Evidence of acute pathological changes of significant proportions was seen in the liver of three of the eight necropsies studied. In two cases in which acute necrosis of the liver was seen, extensive infectious processes were present in addition to the hyperthyroidism. He did not feel that the anesthetic had any bearing upon the liver changes found. The relationship of the liver lesions to thyroid crisis is also discussed. Pathogenesis was thought to be due to exhaustion of the liver cells by the continued severe hyperthyroidism to such a degree that toxic products, which under normal metabolic activity have no effect on the liver, now result in cellular necrosis.

A rather extensive review of the literature on liver changes occurring in hyperthyroidism was made by McIver.<sup>26</sup> It is

reasonable to assume that the liver would feel the increased drive of hyperthyroidism, and the importance of these changes has been emphasized. The occurrence of jaundice in association with the more severe forms of thyrotoxicosis and also disturbances in liver function tests have been frequently noted. Liver changes have also been observed at autopsy. Whether the injury is due to the effects of increased amounts of thyroid hormone on the liver cells, or to the injurious action of some other substance or factor on the liver, which has been made vulnerable by additional strain of hyperthyroidism, is a question. In any case, damage to the liver must be taken into consideration in the clinical management of a case of hyperthyroidism, particularly when the added stress of anesthesia and operation must be faced. A consideration of the possible available therapeutic measures which minimize or prevent liver injury has been reviewed.

While it was pointed out that a diet consisting of high protein and high carbohydrate intake does not afford any specific effect against liver injury, it is important to emphasize the diet from a nutritional standpoint alone, realizing, of course, that all metabolic processes are speeded up in this disease. The vitamin needs are also greatly increased in hyperthyroidism. This is especially true of the vitamin B complex. Special care must be exercised to avoid acute infection in a patient suffering from hyperthyroidism. The anesthetic should be selected for minimum toxic action on the liver and great care exercised to avoid anoxemia. In fulminating cases of hyperthyroidism, the use of local, rather than general, anesthesia should be considered. During the postoperative period, if any evidence of anoxemia develops due to respiratory obstructions or pulmonary complications, prompt oxygen

therapy should be instituted. It was pointed out that hyperpyrexia may contribute to anoxia.

### The Influence of Gastric Surgery on the Liver

Ariel *et al.*<sup>27</sup> studied segments of liver which were removed for chemical analysis as soon as the peritoneal cavity was

Total hepatic lipids increased during surgical intervention. The average increase was 1.97 Gm. per cent. There was a fluctuation in the contents of hepatic protein, with an increase in the hepatic albumin and a decrease in the hepatic globulin during the operation. The physiologic implications of the protein alteration are not apparent.

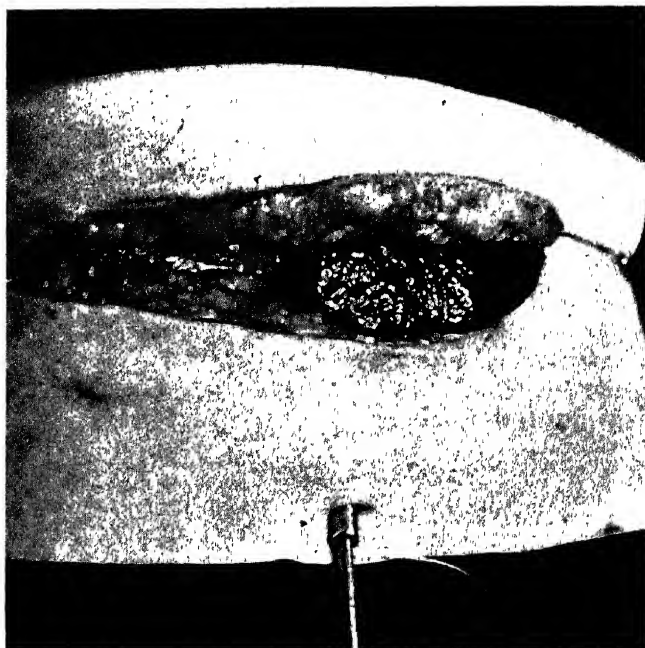


Fig. 10—Liver exteriorized in the abdominal wound previous to suture.  
(W. Wayne Babcock: Surgery.)

entered, and additional samples obtained at the termination of gastric operations on 13 patients. As a result of the chemical analyses of these two specimens, the authors found that there was an average increase of 1 per cent hepatic water during the course of the subtotal gastrectomy. The intravenous administration of fluids during the operative procedures apparently compensate for any fluid loss during the operation. A shift of fluid between the intra- and extracellular positions within the liver occurred during operative procedures on the stomach. An average loss of 45 per cent of the hepatic glycogen occurred during operation.

### External Hepatostomy

Babcock<sup>28</sup> presented a case in which the edge of the liver was exteriorized on the surface of the abdomen for about five months without unfavorable reaction. The exteriorized liver gradually became covered by a film of squamous epithelium derived from the adjacent skin. From the minute ducts opened on the edge of the liver, sufficient drainage of bile occurred to relieve the patient of jaundice and its distressing symptoms. With closure by epithelization of the opened bile ducts, it was possible to obtain additional adequate drainage painlessly and without unfavorable reaction



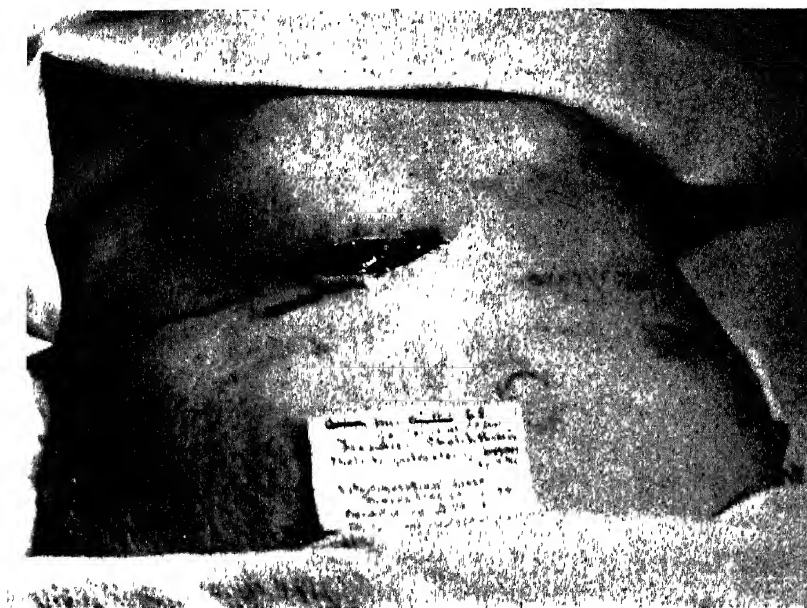


Fig. 11—Exteriorized liver, showing flow of bile 2½ months after external hepatostomy.  
(W. Wayne Babcock: Surgery.)

by incising four wedge-shaped resections of the exposed liver.

Hepatostomy of the exteriorized liver is suggested as a palliative operation to relieve the patient of intense jaundice and associated symptoms of inoperable malignant disease when other palliative measures are unsuccessful. Hepatostomy with or without exteriorization is suggested as a possible first stage procedure for congenital absence or occlusion of the extrahepatic biliary ducts when a single stage anastomosis to the gastrointestinal tract is unduly hazardous.

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## PANCREAS

FREDERICK A. FISKE, B.S., M.D., F.A.C.S.

## Metabolic Studies

Neches *et al.*<sup>1</sup> compare the pancreatic secretion in a group of 30 aged subjects with an average age of 66.5 years with that of a group of 30 young persons with an average age of 23.4 years. Pancreatic secretion was stimulated by the intraduodenal injection of oleic acid, and the following results were obtained:

The bicarbonate and amylase content was significantly increased in the older group. Lipase was 21 per cent lower in the aged subjects. The volume of fluids and trypsin concentration was not significantly different in either group. The authors point out that as a result of diminished salivary secretion, starch digestion is impaired; the slight increase of amylase in the duodenal juice tends to compensate for this deficiency in the saliva. The significant lowering of the lipase secretion by the pancreas suggests that the fat content in the diet of older people should not be high.

A 39-year-old woman presenting a clinical picture of pancreatic insufficiency, who had the duodenum and the head of the pancreas resected and the pancreatic ducts ligated for a carcinoma of the ampulla, was reported by Rekers *et al.*<sup>2</sup> The administration of large quantities of pancreatic enzymes was followed by conspicuous clinical benefits and by a significant decrease in the amount of fat and nitrogen excreted in the feces. An increase in the protein content of the diet resulted in increased absorption of fat. An increase of the fat content of the diet resulted in an increase of the fat absorbed but no lessening of the fat loss. It was found that 87.5 to 95 per cent of the fat and from 39 to 48 per cent of the nitrogen ingested was lost in the feces.

## Tests of Pancreatic Function

In reviewing the contributions to our knowledge of the pancreas and their bearing on the present day ideas of therapy, Whipple<sup>3</sup> stresses the newer clinical tests of the external secreting function of the pancreas, the lipase and amylase determinations in the blood serum for acute lesions, the secretin response in chronic conditions, and the mecholyl determination for the activity of the acinar tissue. During the past five to ten years, surgeons have become more conservative in the treatment of inflammatory lesions and more radical in the surgery of tumors. Moreover, the means of combating jaundice and shock in operations has contributed a great deal to the successful surgery for cancer of the pancreas.

Discussing the various pathological conditions of the pancreas, it was emphasized that in acute pancreatitis the amylase and lipase readings are of the greatest help in making a differential diagnosis. Once the diagnosis is made, the surgeon directs his attention to combating the shock stage of the disease. Many of these patients show such marked improvement in from six to 12 hours, with the mortality reduced to 15 per cent, that delayed conservative surgical management is the optimum choice. In chronic pancreatitis, the surgical advances have not been spectacular. The mecholyl intravenous test is of value in diagnosing chronic lesions from cancer of the pancreatic head with complete obstruction.

In discussing cysts of the pancreas, it was stated that marsupialization or drainage is the surgery of choice. The fistulae which usually develop may frequently be diminished by the installation of a scler-

rosing solution, such as is used in the injection of varicose veins. Should the fistulous tract persist, it is possible to transplant the tract into the stomach or the jejunum.

The majority of the islet cell tumors are microscopically benign adenomas. The syndrome associated with these tumors must present the essential triad: Attacks of disorders of the central nervous system coming on during the fasting state; fasting blood sugar level of 50 mg. per 100 cc. or less, and immediate recovery from these attacks following the administration of glucose by mouth or by vein. Without this triad of symptoms, the diagnosis of a tumor requiring surgery should not be made. When the differential diagnosis of hepatic, adrenal, pituitary, and thyroid disease have been ruled out, surgery is definitely indicated and should not be delayed, because of the enormous carbohydrate intake required and the resultant rapid obesity which adds to the operative risk. Since the thyroid gland may be overactivated by the removal of islet tumors, metabolic study and therapy should always be carried out prior to operation. Transplantation of these rapidly growing cells in a diabetic patient has failed to measure up to the expectations held out for this type of therapy.

Confirmation of the specificity of the serum lipase test is presented by Johnson and Bockus,<sup>4</sup> who from some 1200 determinations utilized for their discussion 21 cases of acute pancreatitis, one of chronic pancreatitis, and 30 of pancreatic cancer. The serum lipase value was above 1 cc. at least once during the course of the illness in 17 (81 per cent) of the 21 cases of acute pancreatitis and in 16 (53.3 per cent) of the 30 with cancer of the pancreas. Analysis suggests that the decrease in serum lipase concentration, following an initial ele-

vated serum lipase, may be due to the subsiding of an inflammatory process or to complete destruction of the pancreas. The serum lipase curve in the one case of chronic pancreatitis was indistinguishable from that in cancer of the pancreas. The serum lipase curve in pancreatic cancer suggests that its initial elevation is due to an obstruction to the free flow of pancreatic juice. The subsequent decrease is due either to replacement of pancreatic tissue by the malignant process, or to impaired pancreatic function secondary to prolonged pancreatic duct obstruction.

### Acute Pancreatitis

Popper<sup>5</sup> points out that most authorities believe that the cause of mild, acute pancreatitis is an entirely different mechanism from that of severe acute pancreatitis. In the mild condition, edema of the pancreas and mild inflammation are present, while in the severe condition, there is fatty necrosis and hemorrhagic necrosis of the pancreas. He was able to produce edema of the pancreas in dogs by injecting into the pancreatic ducts only 0.1 cc. of bile. In the human being a reflux of bile into the pancreas can occur only when the pancreatic and common bile duct form a common channel.

Anatomically, a common channel is difficult to locate; however, during life, entrance of pancreatic juice into the bile ducts is detectable by recovery of pancreatic enzymes in the bile. In 200 surgical cases of gallbladder disease, or other abdominal conditions, bile was aspirated from the gallbladder. Pancreatic enzymes were found in 10 per cent of these cases. Not any of these showed evidence of pancreatic disease. Therefore, it was felt that in 10 per cent of the cases with abdominal pathology, exclusive of pancreatitis, a common channel must exist.

Pancreatic enzymes were isolated from the bile in 16 of the 18 cases of acute pancreatitis, which means that in 89 per cent of the cases of acute pancreatitis a common channel between the bile and the pancreatic duct must have existed. Even though it is generally agreed that bile reflux into the pancreas is the cause of pancreatic necrosis and activation of the pancreatic enzymes, bile is seldom found in the body of the pancreas itself. It was found in only two of the author's 18 cases, in spite of the fact that pancreatic enzymes were found in 16 of the 18 cases. Activation of the pancreatic enzyme may occur either in the pancreas itself following a reflux of bile, or more likely in the ampulla of Vater, or in the bile passages above it, with an extension of these activated enzymes back to the congested secretory ducts of the pancreas and subsequent fat necrosis. Even though a normal biliary system may be found in cases of acute pancreatitis, this need not exclude an extrabiliary system in common with the pancreatic ducts. Popper feels that both the severe and mild forms of acute pancreatitis may be the result of the same mechanism, the difference being only a matter of degree.

Lampson<sup>6</sup> points out that acute pancreatitis is a disease that is difficult to diagnose and easily confused with many acute intraabdominal conditions. In the severe form, it is frequently fatal. The first accurate description and presentation of acute pancreatitis as a clinical entity was given by Reginald Fitz in 1889, when he reported 15 cases with only two recoveries. Wohlgemuth, 1910, reported that in irritative conditions of the pancreas, the pancreatic ferments may be demonstrated in increased amounts in the blood and urine. In 1934, Mikkelsen presented a series of cases of pancreatitis which had been treated conservatively, and in which the mortality was 7.5 per

cent. This percentage was so low, in comparison with the then recognized mortality of from 40 to 50 per cent, that his figures were looked upon with skepticism. Mikkelsen used the diastase test as the main criterion for diagnosis and, therefore, included milder cases in which the diagnosis might otherwise never have been made.

Within a period of a little over three years, 29 cases of acute pancreatitis were reviewed by Lanson. The diagnosis was based upon findings at operation, at autopsy, or on clinical evidence associated with an elevated urinary diastase. The method of diastase determination described by Foged was proven satisfactory. This is based upon the hydrolization of starch by measured dilutions of urine. The mixture is incubated and iodine is added as a means of determining the starch-free tubes. The diastase activity is expressed in units, one of which units is the amount of diastase necessary to hydrolize 1 cc. of 0.1 per cent starch solution under standard conditions. Normal urine shows a diastase activity of less than 300 units. There were no proved false positives, as every patient operated upon in the acute stage of the disease, on whom the test had been made earlier, showed an elevated diastase. It should be emphasized that the test must be made early in the disease, and fresh urine must be used, as the activity of the enzymes deteriorates upon standing.

The severity of the illness varies from a rather mild abdominal upset to an overwhelming and sometimes fatal illness. In the present series of cases, the onset was usually abrupt with upper abdominal pain accompanied by nausea and vomiting. The pain often radiated to the back. In some patients jaundice was present. The physical findings varied in degree, but consisted chiefly of upper

abdominal tenderness and spasm. High epigastric tenderness was present in many cases and not infrequently was associated with tenderness in the left flank. The initial temperature ranged from 99° to 103° F., and the pulse from 60 to 160. The leukocyte count was over 15,000 in nine patients and over 10,000 in 19 patients. The urine analysis was of special interest, as 16 of the 29 patients showed 2 plus and 3 plus albumin, a finding which is not generally emphasized and which undoubtedly reflects the severity of the disease.

Three distinct groups of cases are presented in this series: (1) Patients in whom immediate operation was performed; (2) patients in whom operation was delayed; (3) patients who were not operated upon. Nine were operated upon as an emergency procedure within the first 72 hours of the onset of the illness; ten were operated upon later, from the fourth to the sixteenth day, and ten were not operated upon at all. Death occurred in four cases, a mortality of 14 per cent. Three of the patients who died had been subjected to immediate operation, which represents a mortality of 33 per cent for the group who were operated upon within the first 72 hours. The fourth death was that of a diabetic patient in the nonoperative group who died in uncontrollable diabetic coma. At autopsy, to the surprise of all present, a fulminating pancreatitis was found. In the cases of the nine patients who were operated upon immediately, the correct diagnosis was not made before operation; the preoperative diagnoses were as follows: Acute cholecystitis, four; perforated peptic ulcer, two; chronic cholecystitis, one; twisted ovarian cyst, one; acute appendicitis, one. In the cases of patients who were operated upon later, a preoperative diagnosis of acute pancreatitis was made in the case of one patient, and this was substantiated by the finding

of fat necrosis; in the remaining cases correct diagnoses of acute or chronic cholecystitis were made preoperatively, as in most instances the pancreatitis had subsided at the time of operation.

It was pointed out that there is no doubt that progress has been made in the diagnosis and treatment of acute pancreatitis. It is becoming more and more evident that *operative intervention* in the acute phase of the disease is a hazardous procedure. In the cases subjected to immediate operation, the mortality was 33 per cent as compared with a 5 per cent mortality in patients treated with delayed operation or without operation. *Conservative management* is recommended for acute pancreatitis. The importance of the urinary diastase test as an aid in diagnosis is emphasized.

### Annular Pancreas

To the 48 cases reported in the 1943 Revision Service Volume of THE CYCLOPEDIA OF MEDICINE, SURGERY, AND SPECIALTIES, Chapman and Mossman<sup>7</sup> add another case of annular pancreas. This case was found in the anatomical laboratory on a 50-year-old Greek who had been institutionalized for 11 years with dementia precox. It was impossible to obtain a history of any gastrointestinal disturbance during the man's life. Associated abnormalities were an enlarged spleen, an atrophic imbedded gallbladder with one stone; dense fibrous connective tissue surrounding the common bile duct; two small hemangiomas on the liver; an afferent pancreatic nodule on the dorsal side of the duodenum.

The pancreas was unusually large, measuring 170 mm. from the tail to the right side of the neck. The band of pancreatic tissue completing the annulus was finely fused with pancreatic tissue on both central and dorsal side of the descending part of the duodenum. It meas-

ured 20 mm. in width in front of the duodenum and fanned out on the left side of the latter structure with a width of 45 mm. The length of the lobe making up the band was 100 mm. measured from its origin on the right side of the duodenum to its left ventral termination. This structure definitely constricted the duodenum, and both cephalic and caudal

to the main pancreatic duct dorsal to the duodenum. What was probably a small accessory duct of Santorini was also observed connecting with the main duct to the duodenal wall.

The most logical explanation for annular pancreas seems to be a persistence of the left, as well as the right, ventral pancreatic duct.

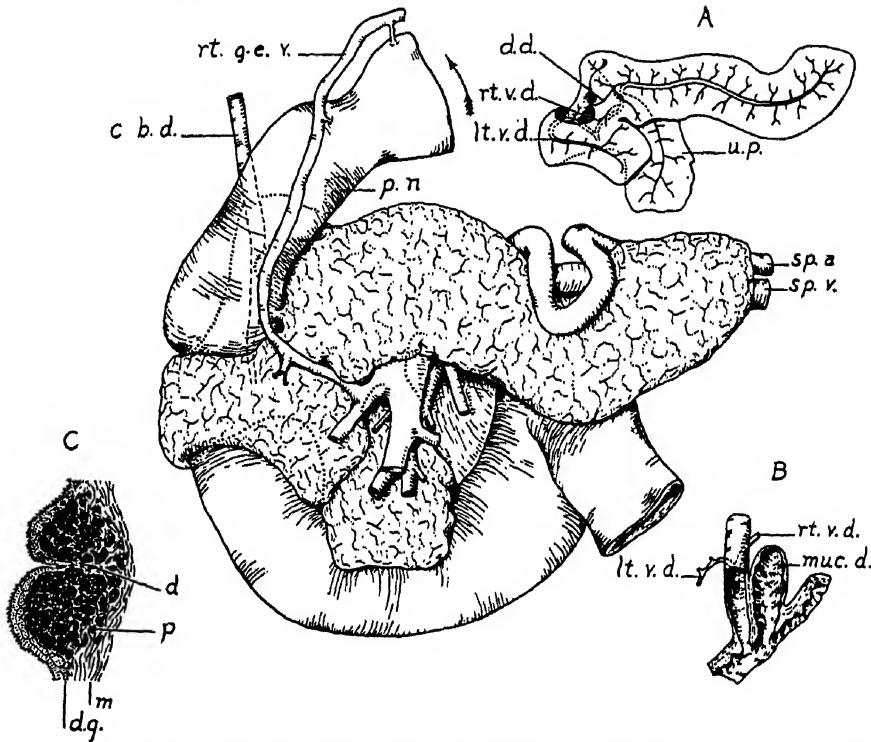


Fig. 1—Ventral view of ring pancreas showing relation to duodenum and superior mesenteric and splenic vessels. First part of pylorus and duodenum rotated upward as indicated by arrow. Mesenteries and superior pancreaticoduodenal vessels not shown. *A*, Diagram of pancreatic ducts. *B*, Duodenal end of the common bile duct and the proximal portions of the right and left ventral pancreatic ducts, showing their relation to the mucosal diverticulum and the wall of the duodenum. There was no papilla major. *C*, Diagram of a section through the pancreatic nodule in the wall of the first part of the duodenum. (Main figure is one-half size; others not drawn to scale.)

*c, b, d*, Common bile duct; *d*, duct in pancreatic nodule; *d. d.*, dorsal pancreatic duct (accessory or Santorini's); *d. g.*, duodenal glands (Brunner's); *lt. v. d.*, left ventral pancreatic duct, the one normally absent; *m*, muscle layer of duodenum; *muc. d.*, mucosal diverticulum; *p*, pancreatic tissue; *p. n.*, location of pancreatic nodule in duodenal wall; *rt. g-e. v.*, right gastroepiploic vein, continued below as the inferior pancreaticoduodenal; *rt. v. d.*, right ventral pancreatic duct (main or Wirsung's); *sp. a.*, splenic artery; *sp. v.*, splenic vein; *u. p.*, probably a much enlarged uncinate process. (J. L. Chapman and H. W. Mossman: *Am. J. Surg.*)

to the ring the latter was dilated. The duct system of the pancreas revealed a duct from the annular portion which joined the main duct of Wirsung just before the latter entered the common bile duct. Several ducts in the region of the head were found to contribute branches

### Cysts of the Pancreas

Bowers *et al.*<sup>8</sup> report five cases of cystadenoma of the pancreas, which were treated surgically. Four of the five patients had a definite history of antecedent biliary tract disease. Two of these patients also noted the presence of an

abdominal mass. All five of the patients were women, whose ages ranged from 37 to 66 years. A palpable and sometimes visible mass was the most important physical finding, being present in four of five cases. It was movable in two cases and fixed in two cases. Tenderness was present in one case and this was due to leakage of the contents of the cyst. Mild to moderate diabetes was present in two cases, normal urine and blood sugar in two cases. The severity of the diabetes was increased shortly after operation in the two cases observed.

Roentgen examination was of diagnostic value in four of the five cases, showing a soft tissue mass in the upper left abdominal quadrant, which in one case was distinguishable from the shadows of the kidney and spleen. Gastrointestinal roentgenogram showed definite displacement of the stomach, in varied positions, in four cases. Barium enemas showed caudal displacement of the transverse colon in four cases. Intravenous pyelograms, made in two cases, showed normal shadow in one and incomplete findings of the pelvis in the other. This was probably due to the pressure of the cyst on the renal vessels as postoperative pyelograms were normal.

At operation, a dilated cystic vein was found intimately associated with the wall of the cystadenoma of the pancreas in three cases. In one case, it was necessary to remove a greatly enlarged spleen; in another, injury to this vein resulted in death of the patient from hemorrhage and shock.

The cysts were all smooth, well encapsulated, multilocular, and filled with clear or turbid fluid. Two cysts arose from the body, and two from the tail of the pancreas. Microscopically, the cyst lining was of high columnar or cuboid epithelium, with clear cytoplasm and ba-

sal nuclei. The lining was thrown into papillary projections.

Rabinovitch and Pines<sup>9</sup> record a series of 17 cases of cysts of the pancreas. In 14 cases, operation was performed. The operating surgeon had difficulty in identifying the relationship of the cyst to surrounding structures and was unable to determine whether it was a true pancreatic cyst or a so-called pseudocyst in some cases. In one case the tumor was malignant. Pancreatic cysts may occur at any age; however, they are more common in middle age. In the series reported, the age ranged from 21 to 66 years, averaging 45.4 years. There were 14 female and three male patients. The opinion that pseudocysts are more common than other cystic tumors of the pancreas was borne out in this series. The cyst was more prevalent in the tail of the pancreas. It was felt that trauma was the etiologic factor in most cases. Pseudocysts may also develop following certain inflammatory conditions of the pancreas or gallbladder. In other cases, a cause cannot be determined. From an embryologic viewpoint, it was conceivable that certain pancreatic cysts may arise from misplaced remnants of Brunner's glands.

The diagnosis of these tumors is at times difficult. The early symptoms and signs are not distinctive and are similar to those associated with other intra-abdominal lesions. The laboratory tests, although of great value, are by no means infallible. Analysis of the diagnostic facts relating to this disease show that pain is the most important objective symptom. It was present in all of the operative cases, and varied from a sensation of fullness to sharp abdominal cramps. The location of the pain varied. In many instances pain was associated with nausea and vomiting. Loss of weight occurred in six of the patients

operated upon, constipation in five, diarrhea in two. Jaundice occurred in three patients.

Physical examination revealed that ten patients were well nourished, that two were obese, and that two were emaciated. Only three patients appeared acutely ill on entering the hospital. Tenderness over the affected area was elicited in five patients. Pseudocystic tumor usually presented itself as a large semifluctuant mass. In four cases it was located in the left upper quadrant of the abdomen; in three in the right upper quadrant of the abdomen; in two the lower part of the abdomen, and in one case the mass occupied the entire left side of the abdomen. The cysts are more apt to be freely movable when situated in the tail of the organ. Roentgen examination is a major aid in the diagnosis of cyst of the pancreas. An enlarged duodenal curve is characteristic of enlargement in the region of the head of the pancreas. Displacement of the duodenum and the small intestine points toward diagnosis of cyst of the pancreas.

The preoperative diagnosis was cyst of the pancreas in four cases and carcinoma of the pancreas in two cases. In the remaining cases the preoperative diagnosis was retroperitoneal tumor, omental or pancreatic cyst, ovarian cyst or fibroma of the uterus, peptic ulcer, acute pancreatitis, acute cholecystitis, chronic appendicitis, and retroperitoneal sarcoma or cyst of the pancreas. The pathological picture presented at operation is characteristic. The large cyst arising from the region of the pancreas is so striking that one can scarcely fail to diagnose the condition at operation, after having once viewed the lesion. The tumor usually presents itself as a smooth, relatively immobile, semispheric, and semifluctuant swelling, which arises in the region of the pancreas. The size of the tumor

varies from 5 to 30 cm. in diameter.

The existence of pancreatic secretions in the cysts has been frequently noticed. On the other hand, numerous instances of true cysts are on record in which no ferments were found. The absence of ferments appears to be of relatively little value in confirming or excluding the diagnosis of pancreatic cyst. Chemical analysis of the aspirated fluid in this series revealed that ten of the examined specimens showed the presence of trypsin, amylase, or of both. In six instances no chemical analysis was done, and in the case of pseudocysts with carcinomatous changes, no enzymes could be found in the aspirated fluid. Some of the cysts contained mucus, fats, bile, and lipase.

The choice of operation depends on the size, variety, location, and condition of the cyst. The ideal treatment is complete removal. Small cysts, especially in the tail of the pancreas, should be excised. In cases in which the cyst is large and adherent, marsupialization of the tumor is believed to be the method of choice.

Ormond *et al.*<sup>10</sup> present three case studies with an original urological diagnosis, but at operation it was found that the true nature of the condition was a cyst of the pancreas. It was pointed out that some six additional cases of this type have been recorded in the literature.

It was noted that this antecedent pathology of the pancreas can and does cause an occasional renoureteral distribution of pain and that urinary changes, especially hematuria, are not at all unusual. The first case reported simulated a retroperitoneal tumor, the second a perinephritic abscess, and the third case was operated twice before it was certain that the cyst was entirely unrelated to the kidney. Case histories with pyelograms are given in the detailed article.



### Cystic Fibrosis of the Pancreas

Attwood and Sargent<sup>11</sup> point out that cystic fibrosis of the pancreas is not very uncommon, although its diagnosis in the living is unusual. It may be missed at autopsy if sections of the pancreas are not taken for microscopic study. The etiology of the changes in the pancreas may not be definitely discovered. The associated pathological changes in the lung may overshadow the fundamental pathological process of the pancreas.

The roentgen appearance of the pulmonary lesion is that of purulent bronchitis with bronchiectasis, bronchohepatic abscess formation, and surrounding pneumonia. These changes may occur in patients who are not suffering from pancreatic disease. The authors state that six features may suggest the presence of an associated disease of the pancreas; they are as follows:

1. In a typical case of cystic fibrosis of the pancreas the pulmonary changes are diffuse, and they involve all lobes of both lungs but are most marked in the region of the hilum. The hilar shadows are increased in density, with loss of definition, and extend outward into a surrounding mottling which gradually diminishes towards the periphery of the lung.

2. The marked chronicity of the pulmonary lesion is a striking feature and may lead to an erroneous diagnosis of tuberculosis.

3. Although atelectasis was seen in only one of the four cases reported, the large amount of purulent, tenacious exudate present would be expected to produce atelectasis.

4. Bronchiectasis is present in a large number of cases of this disease but a definite demonstration is dependent upon the injection of an opaque medium which was not done in any of the four cases presented.

5. There is evidence of abnormal intestinal motility as indicated by the presence of gaseous distention and fluid levels.

6. The average age at onset is apparently two to three months and most of the infants die before they reach the age of two years.

### Pancreatic Fistula

Comfort *et al.*<sup>12</sup> report certain physiological observations made in a case of external pancreatic fistula in which cure was effected surgically. Fasting secretion of pancreatic juice, which came through the external fistula when the pancreatic juice was excluded from the duodenal cavity, was low in volume and in total bicarbonate and enzyme content.

The fasting secretion of pancreatic juice, which came through the external fistula when the gastric juice was allowed to enter the duodenal cavity, was variable but, for the most part, it was low in volume and bicarbonate content.

Secretion of pancreatic juice, which came through the external fistula when gastric juice was excluded from the duodenum, was not measurably stimulated by glucose and casein, and was only slightly stimulated by olive oil introduced through the duodenal tube into the duodenum.

The secretion of pancreatic juice which came through the external fistula was stimulated vigorously by glucose and casein administered orally. The effect of glucose and casein was similar to that obtained by the administration of purified secretin; they effected an increase in volume and an increase in the total secretion of bicarbonate, amylase, and lipase. The secretion of pancreatic juice which came through the external fistula and its contents of bicarbonate and lipase was not stimulated and was probably depressed by olive oil administered orally;

the secretion of amylase, on the other hand, appeared mildly stimulated. The secretory response in regard to the volume of bicarbonate and of enzymes seemed to depend, first, on the gastric secretory response to food and the emptying time of the stomach and, second, on the effect of the gastric secretion on the secretin mechanism. The type of secretory response did not appear to depend as much on the effect that food exerts directly on pancreatic secretion as on the effect of food on the gastric secretion. Gastric contents (gastric secretion plus food) was a much more potent stimulant of pancreatic secretion than were foods alone.

The secretion of pancreatic juice which came through the external fistula, after the administration of mixed meals, depended on the proportion of the different foods present in the meal. Meals low in fat and high in carbohydrate and protein stimulated a greater flow of all components of pancreatic juice than did meals high in fat.

### Pancreatic Stones

Moss and Freis<sup>13</sup> point out that pancreatic lithiasis is not as rare as was formerly believed. From 1934 to 1941, three cases were observed in Boston City Hospital. During 1941, three cases were recognized among 700 autopsies, and two cases were observed clinically. The latter two are reported. In one case, the diagnosis was made by roentgenogram; in the other the roentgenographic findings were confirmed by palpation of the pancreas at laparotomy. Pancreatic ferments of these patients were studied before and after stimulation with mecholyl. The lipase and amylase activity were in the normal range and showed a significant increase after stimulation with mecholyl. The results of these tests indicate that some degree of pancreatic dam-

age was present. There was no conclusive evidence that either of the patients had ever suffered from acute pancreatitis. One patient had cholelithiasis and diabetes mellitus, and the other had a decreased glucose tolerance and an enlarged liver that showed improvement with the use of lipocaic. Steatorrhea was not present in either case.

The clinical diagnosis is difficult, but is often missed because pancreatic lithiasis is not thought of. Upper abdominal pain is usually the leading symptom, varying from mild distress to severe colic that resembles biliary colic. The pain is likely to be referred to the left side of the abdomen, back, or to the left shoulder. Nausea and vomiting may be severe. Attacks seem to be induced by fatty foods and alcoholic excess. Fatty diarrhea is the most characteristic sign of the disease, but is present in only one-half of the cases and may be intermittent. A late sign of pancreatic damage is liver enlargement. Diabetes mellitus accompanied by abdominal pain of obscure origin should point to the possible existence of this disease. A flat film of the abdomen may reveal the calculi. The chief difficulty in the clinical diagnosis is the frequent absence of unmistakable signs of pancreatic insufficiency. To facilitate the diagnosis in the absence of steatorrhea, the use of pancreatic stimulants, such as secretin or mecholyl, gives a roughly quantitative estimate of the pancreatic output.

Although neither of these patients were treated surgically, the principal or the primary treatment of this disease is surgical. **Removal of the obstructing stones** has been successfully carried out to rid the patient of symptoms and to halt further destruction of the pancreas. Symptomatic treatment consists of the use of **dried pancreatic juice**. The colic is usually treated with **morphine**, al-

though *ephedrine* is worthy of trial because it diminishes the pancreatic secretion. *Lipocaic* may be of specific value in the treatment of the associated fatty liver.

### Carcinoma

Phillips<sup>14</sup> states that 65 patients have had radical surgery for carcinoma of the ampulla, including the case he reports.

This patient had a cholecystostomy performed for a gangrenous ruptured

creas were removed in one block. The large end of the stomach and the duodenum near the ligament of Treitz were closed. The pancreatic duct was ligated and the head of the pancreas was sutured in the jejunum.

The author proposed using a rather long loop of jejunum to anastomose the common duct as a first stage, and after extirpation of the duodenum and head of the pancreas, this can be swung over

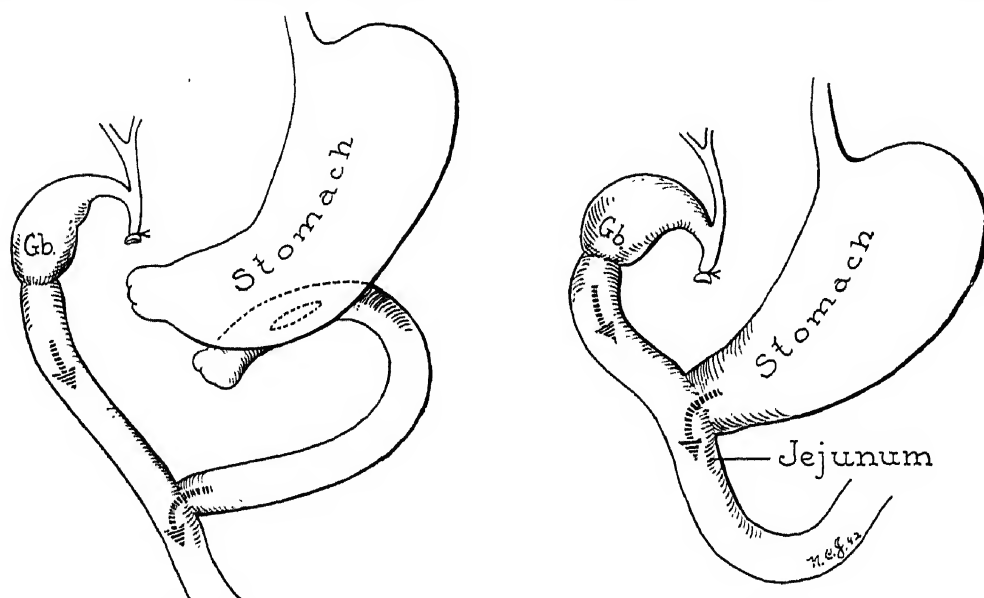


Fig. 1.—A diagrammatic line drawing in which the anastomoses done in the two-stage operation of Whipple (a) left, is compared with the simplified anastomosis (b) right, herein described. Note that the physiological principles of both are the same. (H. E. Pearse: Surg., Gynec., and Obst.)

gallbladder. Following this, the patient passed no bile into his intestinal tract. At a second operation, the common duct was found markedly dilated, and a soft mass could be felt at the end of the scoop at the ampulla. Upon opening the duodenum, a tumor mass was seen, which on section proved to be a Grade II adenocarcinoma. The tumor was destroyed by *cautery* and the duodenum closed. The common duct was anastomosed to the stomach above the pylorus, the gallbladder removed, and an *anterior gastroenterostomy with entero-anastomosis* performed. After six weeks the duodenum and the head of the pan-

creas were removed in one block. The large end of the stomach and the duodenum near the ligament of Treitz were closed. The pancreatic duct was ligated and the head of the pancreas was sutured in the jejunum. The author proposed using a rather long loop of jejunum to anastomose the common duct as a first stage, and after extirpation of the duodenum and head of the pancreas, this can be swung over

and a biopsy taken, many operable lesions will be overlooked. Opening the duodenum was urged in all doubtful cases.

A method of *one-stage resection* of the duodenum and head of the pancreas was described by Pearse,<sup>15</sup> which restores the continuity of the biliary and

to cut the ligament of Treitz and in some cases divide vessels to the first part of the duodenum before the duodenum may be removed. The end of the jejunum is anastomosed to the gallbladder and the stomach is anastomosed to the side of the jejunum. The one-stage procedure is applicable only in good risk patients.

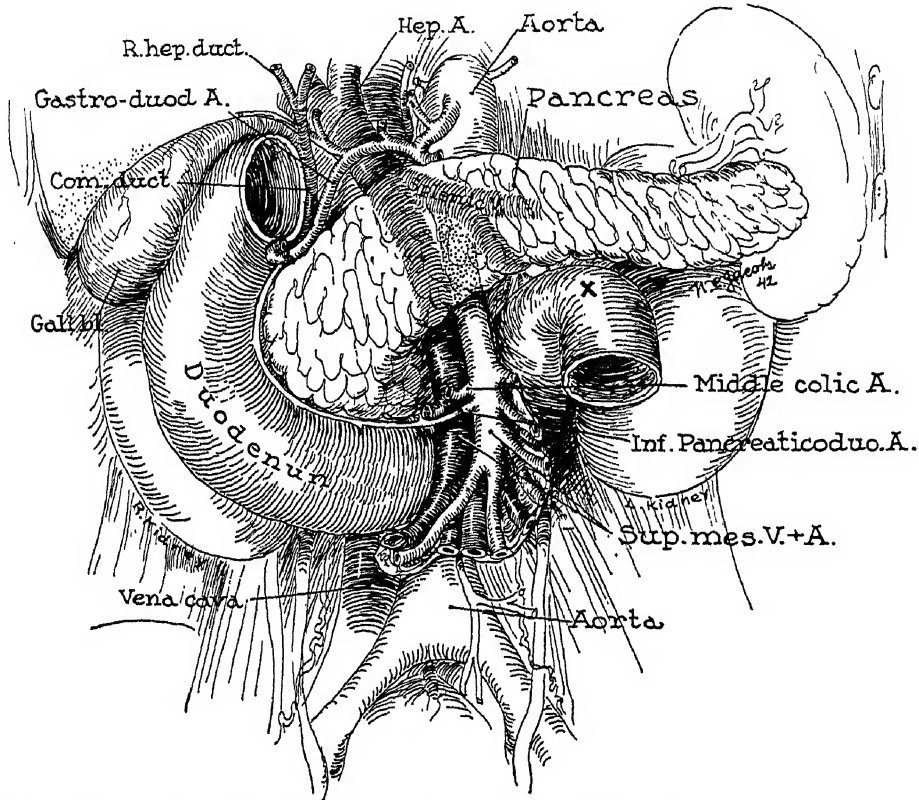


Fig. 2—The anatomy of the dissection is shown. When Treitz's ligament is cut and the vessels supplying the fourth part of the duodenum are ligated, the bowel will slip under the superior mesenteric and middle colic vessels. It is easy to do this if the inferior pancreaticoduodenal artery is first ligated and these vessels are lifted up off the duodenum with a retractor. This also assists in exposing the uncinete process of the pancreas. The bowel is divided at X and the distal portion brought up to anastomose with the gallbladder. The pancreas is divided just in front of the superior mesenteric vein. (H. E. Pearse: Surg., Gynec., and Obst.)

digestive tracts with only two anastomoses. This technic retains the advantage of an antiperistaltic intestinal biliary union, but in a simplified form.

According to the author, the anastomosis described is applicable only if the operation is done in one stage and the entire duodenum removed. In this case, and several cadavers, it was possible to roll the duodenum from beneath the superior mesenteric vessels. It is necessary

According to Babcock,<sup>16</sup> *single clamp method* for resection of the head of the pancreas for cancer has the advantage of eliminating soiling of the wound field by bile or gastrointestinal contents, which activate pancreatic ferments, and also of simplifying a one-stage operation. The lower part of the stomach, the duodenum, and the head of the pancreas are liberated en masse, the common bile duct is divided between ligatures, and the

duodenum is divided near its third portion by cautery between clamps. The pancreas is divided and the retained end is closed with ligatures and sutures, and covered by omentum. The liberated portion of the stomach, the duodenum, and pancreas is turned out of the abdomen. The distal end of the duodenum is closed by inverting sutures with removal of the clamps, and the fundus of the gallbladder is liberated. The posterior surface of the duodenum, about 1 cm. from the ligament of Treitz, is sutured across the posterior surface of the stomach. The liberated fundus of the gallbladder is sutured on the anterior surface of the attached jejunum, just below its antimesenteric border. A single clamp now is applied across the stomach, jejunum, and gallbladder, now a segment of the last two with adequate lumina projecting above the clamp. A second clamp is applied across the stomach 5 mm. above the first, and the stomach is divided between the clamp and the projecting folds of jejunum and gallbladder are burned off with cautery. A continuous suture is then introduced over the clamp between the anterior surface of the stomach above and the anterior surfaces of the gallbladder and the jejunum below, which is tightened as the clamp is withdrawn.

Additional anterior sutures are used to reinforce the anastomosis and further to invert the gallbladder and edge of the jejunum into the stomach. The stomach and attached segment of jejunum are then invaginated with the thumb and finger to open the stomas. Obviously the gallbladder may be applied lateral or posterior to the loop of jejunum.

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## THE STOMACH

FRANCIS L. ZABOROWSKI, M.D.

### Gastric Ulcer

For many years the treatment of gastric ulcer has been the subject of considerable discussion and controversy. Some physicians have been enthusiastic regarding medical treatment, whereas certain surgeons have been equally in favor of surgical treatment in the large majority of cases. It would seem that

this subject should be pretty well settled after the extensive clinical experience which has been amassed in the management of this condition. However, confusion still persists regarding the ideal choice of therapy in many of these cases.

The important questions which must be answered before definite opinions can be reached include: (1) What is the

percentage of error in the diagnosis of benign gastric ulcer, when actually a small ulcerating carcinoma is present? (2) what is the percentage of cure of gastric ulcer treated medically? (3) what is the risk of operation for gastric ulcer? (4) what is the rate of ultimate cure of this lesion by surgical measures?

Accurate answers to these questions should enable one to determine whether the risk of operation and chance of cure by surgical means are preferable to the chance of diagnostic error and likelihood of unsatisfactory results by medical measures. It is realized that generalizations often are misleading and unreliable for the individual patient, as obviously the choice of treatment must remain largely a matter to be decided for each individual patient; nevertheless it is helpful to know what the odds favor, so to speak. For this reason Judd and Priestley<sup>1</sup> have attempted to find answers to the questions listed.

#### **Accuracy of Clinical Diagnosis—**

As everyone realizes, an entirely accurate differential diagnosis cannot always be made between benign and malignant gastric ulcer. To concede this point one need not have any firm conviction regarding the pathogenic relationship between these two entirely distinct entities, and this subject will not be discussed at this time. It is sufficient to admit that certain small ulcerating carcinomas of the stomach may present a clinical picture which cannot be distinguished from that which may be found in association with benign ulcer. The main differential points between benign and malignant gastric ulceration, such as age of the patient, duration and type of symptoms, size and location of the lesion, achlorhydria or hyperchlorhydria, roentgenologic and gastroscopic appearance, and response to medical treatment may in certain cases all be misleading. Thus,

examples can be cited from personal experience wherein all factors, such as youthful age of the patient, long history of typically ulcer-like character, small lesion situated on the lesser curvature associated with high values for gastric acid, a roentgenologic and gastroscopic diagnosis of benign ulcer and a favorable and immediate response to medical management, favored the diagnosis of benign ulcer, but notwithstanding the patient subsequently was found to have an actual carcinoma. Likewise the reverse may be true, whereby the results of clinical investigation all suggest the malignant nature of the lesion and a benign ulcer is demonstrated histologically. It is true that such occurrences are not common but in a small percentage of cases the majority of factors may favor one diagnosis and yet the diagnosis based on these findings may be erroneous. The tragedy of permitting a small, readily resectable, malignant lesion of the stomach to progress to the stage of inoperability or to the time when prognosis is much less favorable, even though resection can be accomplished, because of postponement of operation by the initial medical treatment need not be emphasized.

A few reported observations on the difficulty of distinguishing between benign gastric ulcer and actual gastric carcinoma might be pertinent. For example, approximately 7 per cent of patients who undergo resection for malignant growths of the stomach are less than 40 years of age. Eighty per cent of patients who have gastric resection for malignant tumors and who previously received medical treatment for presumed benign ulcer experienced temporary relief from this form of therapy. Approximately one of five patients who has gastric resection performed for cancer has normal or elevated values for gastric

acids. Although nine out of ten benign gastric ulcers which are removed surgically are smaller than a quarter, it has been noted that approximately one-fifth of the carcinomatous lesions removed from the stomach have an area of ulceration 4 cm. or less in diameter. Over a period of many years the diagnosis of gastric ulcer has been made by the roentgenologist in approximately 10 per cent of cases in which resection has been performed for actual carcinoma.

Thus it is emphasized again that there is no single clinical criterion which can make an accurate differential diagnosis between benign and malignant gastric ulcer. The only method of certain differentiation is prolonged observation under medical treatment. Such observation should be carried on (intermittently following the first several months) for a period of at least several years. If the lesion disappears promptly and remains absent roentgenologically and gastroscopically for this period of time, one would feel fairly confident that it is benign in nature. Of course, should it prove to be malignant during this interval, the optimal time for surgical treatment, namely, when the lesion was in an early stage of development, would have been lost.

What then, in answer to the first question proposed, is the actual error of diagnosis in benign ulcer? This may be approached in two ways, first, the percentage of error found in cases in which patients are treated surgically and, second, the percentage of error found in cases in which patients are treated medically. A recent review revealed that carcinoma was found on exploration in 19, or 8 per cent, of 237 cases in which a diagnosis of benign gastric ulcer was made and operation was performed at the Mayo Clinic during 1939 and 1940. As a corollary, in a series of 559 cases

in which operation was performed for gastric carcinoma during this same period, the diagnosis in the 19 cases mentioned here was gastric ulcer. In order to determine the results of the medical treatment of gastric ulcer, of which more will be said later, 146 patients whose condition was diagnosed as benign gastric ulcer between the years 1930 and 1937, and who were treated medically, were traced to the present time. Of this group it is known as 14 patients, or 9.6 per cent, subsequently were shown to have gastric carcinoma. This observation is supported by the findings of others, including Allen and Welch, who reported 277 cases in which the diagnosis of benign gastric ulcer was made. Thirty-nine, or 14 per cent, of these patients later were known to have carcinoma. Some were treated medically and others surgically. Of the 175 patients in this group who were treated medically, 13, or somewhat more than 7 per cent, subsequently were found to have carcinoma. Considering the chance of diagnostic error based on clinical criteria from these various points of view, it is evident that approximately once in 10 or 12 times the clinical diagnosis of benign gastric ulcer will be in error, and in truth carcinoma will be present.

**Results of Medical Treatment**—A recent study has been made concerning the second question, namely, what are the results of medical treatment of benign gastric ulcer? Cases in which the diagnosis of gastric ulcer was made in the Mayo Clinic during the years 1930 to 1937, as previously mentioned, have been reviewed. There were 146 cases in this group which filled the necessary requirements for the study, namely, a complete examination was performed, the diagnosis of gastric ulcer made, medical treatment was instituted, and knowledge of the present condition of the patient was



obtained. Of the 146 cases, cure occurred in only 46.5 per cent. An additional 15.8 per cent of the patients had no symptoms if the medical regimen was followed constantly; 4.8 per cent were found to have gastric ulcer by roentgenologic diagnosis; 11 per cent were operated on because of failure of medical management and found to have gastric ulcer and 9.6 per cent (14 patients) presented definite evidence of gastric carcinoma. Of this group of 14 patients one-half died of metastatic carcinoma and the remainder were explored surgically; however, in only three cases could the gastric cancer be removed. Eleven and six-tenths per cent of the entire group of 146 patients died of apparently unrelated causes and 0.7 per cent (one patient) died of gastric hemorrhage.

Analysis of these results indicates that the medical treatment of presumed benign gastric ulcer leaves considerable to be desired. With cure accomplished in somewhat less than 50 per cent of cases and with approximately 10 per cent of patients subsequently manifesting frank carcinoma of the stomach, one could hardly call the results eminently satisfactory. In addition, 11 per cent of the patients required operation subsequently for benign gastric ulcer because of failure of medical management. One need operate on only a few penetrating gastric ulcers which have eroded completely through the wall of the stomach and have a crater, the base of which is formed perhaps by the pancreas, to appreciate the difficulties inherent in effecting complete healing of the lesion by medical measures. In addition, the marked degree of gastritis and inflammatory activity of a benign gastric ulcer so often seen at the operating table following intensive medical treating for several weeks in the hospital prior to operation serve to emphasize the ineffectiveness of medi-

cal management in many of these cases.

**Risk of Surgical Treatment** — In contrast with results obtained by the medical treatment of gastric ulcer, what may be expected from the surgical treatment of these patients? The first question to consider in this regard is the risk of operation. This, of course, will vary with the condition of the patient, experience of the surgeon, type of operation performed, and preoperative and postoperative care. During the past five years at the Mayo Clinic the risk of gastric resection performed for gastric ulcer in 400 cases has been 2.5 per cent. During this same time the risk of local excision and gastroenterostomy for gastric ulcer has been 3.3 per cent.

**Ultimate Results** — In the authors' experience resection of the stomach for gastric ulcer is followed by some of the most satisfactory results that are obtained in the surgical treatment of any gastric or duodenal lesions. Walters and Clagett in 1940 reported on 272 cases of gastric ulcer treated surgically. Follow-up studies over a period of one to five years were obtained in 162 cases. There was no known incidence of the development of gastrojejunal ulcer, and only one patient in the entire group classified his result as entirely unsatisfactory. Of 29 patients followed on whom local excision combined with gastroenterostomy was performed, 27 had an entirely satisfactory result and two had mild distress at times. Of 85 patients on whom a Polya type of resection was carried out, 80 had an entirely satisfactory result and five were in good health but had an occasional slight distress. Information in some of these cases was obtained by questionnaire which may be considered unreliable; however, it is seldom that a patient will write that he is well unless he actually feels well. The length of follow-up period may be a little short for an

accurate analysis of the true ultimate results, and yet it coincides quite closely with their experience. Other procedures, such as local excision alone, sleeve resection or gastroenterostomy alone, are followed by somewhat less satisfactory results.

**Choice of Operation**—The surgical treatment of choice in most cases of gastric ulcer is gastric resection. For the lesion situated in the distal third of the stomach, a *Billroth I type of operation* can be employed with satisfaction in some cases. In general, the *posterior Polya operation* is the one which the authors employ most frequently. When dealing with an ulcer situated high on the lesser curvature of the stomach, the *Hofmeister modification of the posterior Polya operation* is often most satisfactory. Occasionally, if the lesion is especially high, an anterior type of *anastomosis without enteroanastomosis* is employed. This type of operation, however, is used only infrequently. Modifications of this procedure may be employed for an ulcer situated in the cardia on the anterior or posterior walls of the stomach.

### Acute Gastroduodenal Perforations

During an 11-year period (1930-1941) at the Metropolitan Hospital there were 89 perforated peptic ulcers. Of the patients admitted 34 gave a definite history of ulcer history and 29 a history highly suggestive of ulcer. Ten of these 63 perforated while under treatment in the hospital. Not included in this series was an 11-month-old male infant successfully operated upon for a perforated peptic ulcer.

The story of the present illness leads one to suspect the diagnosis in nearly every case. The patient may state that shortly after the ingestion of a meal or liquids, while lifting or straining he was

suddenly and violently seized with an agonizing pain. The pain may be described as burning, lancinating, or knife-like. It frequently starts in the epigastric region and rapidly spreads throughout the abdomen, particularly if located on the anterior surface near the pylorus. When the perforation is on the anterior surface of the duodenum, fluid gravitates to the right lower quadrant and this pain may be confused with that of acute appendicitis. Perforation through the posterior gastric wall into the lesser sac occurs infrequently, but this pain may simulate the colicky pain of intestinal obstruction. Perforated gastrojejunal ulcers and perforations on the lesser curvature may give rise to predominantly left-sided symptoms. Shoulder pain, either right or left shoulder or both shoulders, is highly suggestive. When the abdomen is palpated the outstanding feature is the boardlike rigidity. Palpation elicits exquisite tenderness, rebound tenderness, and skin hyperesthesia. Percussion for fluid in the flanks is of little value for early diagnosis of perforation. Demonstration of diminished liver dullness is pathognomonic of a ruptured viscus but it cannot be elicited in every case. There is exquisite rectal and vaginal tenderness. The abdomen is silent to auscultation. Temperature is normal or subnormal in the early stages. The pulse may be little altered. Leukocytosis occurs early with a shift to the left. The presence of subdiaphragmatic air as shown by the roentgenogram is pathognomonic of a ruptured viscus. When the roentgenogram fails to show the presence of subdiaphragmatic air it is imperative that blood be drawn and an estimation made for serum amylase. This will rule out acute pancreatitis. Peritoneal aspiration is diagnostic and relatively devoid of danger. The puncture is performed in both right upper and right lower quadrants of the

abdomen using a spinal needle and syringe. When peritonitis is due to a perforated peptic ulcer under 12 hours' duration mucinous material, bacteria, and cholesterol crystals will be present. In later cases, fiber shreds and cholesterol crystals are seen. Five to 10 per cent of cells present are eosinophilic polymorphonuclears. Diagnosis of ruptured viscus may be facilitated by giving the patient 30 to 50 cc. of a dilute methylene blue solution by mouth or introduction through a Levin tube one-half hour prior to peritoneal aspiration. When the diagnosis is established a Levin tube is passed and continuous siphonage maintained with the Wangenstein suction system preoperatively, throughout the operation, and postoperatively. Blood is obtained for typing and cross matching, and when indicated to combat shock or dehydration intravenous fluids are given preoperatively. Spinal anesthesia is preferred. Odom and DeBakey report lower mortality rates with spinal than with inhalation anesthesia. The majority of surgeons do not favor radical operation for the acutely perforated ulcer. Forty-eight patients<sup>2</sup> had simple plication; the mortality was 22.4 per cent. As soon as the peritoneum is opened culture of its contents should be taken and all excess peritoneal fluid gently suctioned off. The point of perforation is determined and plication should proceed with interrupted Lembert No. 00 or No. 000 chromic sutures on an atraumatic needle. The sutures should be placed in the long axis of the gastrointestinal tract to plicate the perforation transversely to the long axis to avoid further stenosis of the pylorus. As a further safeguard gastrohepatic or gastrocolic omentum may be tacked to the suture line. During the last two years the practice of draining the peritoneal cavity for perforated peptic ulcer has been abandoned at the Metropolitan

Hospital. The authors use drains only when a localized abscess is present. Locally, 8 Gm. (120 grains) of *sulfanilamide* and 4 Gm. (60 grains) of *sulfathiazole* are used if the perforation has been present for more than six hours. The wound is not drained. Because of the high incidence of wound complications they now plan to close the abdomen in layers, using interrupted alloy wire sutures.

*Gastroenterostomy* is usually done when the surgeon believes that pyloric stenosis is present to such a degree that pyloric obstruction will become necessary. Rather than perform gastroenterostomy at time of perforation it would be better to thread an Abbot-Rawson or Levin tube through the pylorus for postoperative feeding.

During recent years, *subtotal gastric resection* performed at time of operation for perforation has been advocated. It has been performed in selected cases and has yielded excellent results.

The postoperative care requires meticulous attention to details. Wangenstein suction is continued for 72 hours. When the Abbot-Rawson tube is utilized, jejunal feedings can be instituted six hours postoperatively. When the Levin tube is used nothing is given by mouth for the first 24 hours. During this period the patient receives 2500 cc. of a 5 per cent *dextrose solution in physiological saline*. *Whole blood or plasma* is given when indicated by hematocrit readings. After 24 hours 15 cc. of warm water are given orally every hour for 12 hours and then 30 cc. every hour for 12 hours, clamping off the tube for one-half hour after administration. Ten cubic centimeters of physiological saline are instilled through the tube every hour to insure its patency. Again parenteral fluids are given during this period. Frequent change of position, movement

of the extremities, and forced inspiration every hour aid in avoiding postoperative complications. *Oxygen* is given and continued as long as there is danger of anoxia.

More than 50 per cent of the patients exhibited definite hypoproteinemia. Estimations conducted on 18 patients exhibited low ascorbic acid blood levels but none reached a scurvy level.

### Gastroileostomy and Gastroileal Ulcer

There are several complications which may follow gastroenterostomy. When a patient has had a previous gastric operation presents himself with symptoms referable to the gastrointestinal tract, it is well to analyze the complaints carefully with all the possibilities in mind. The syndromes representing gastrojejunitis, gastrojejunal ulcer, malfunctioning gastroenteric stoma, and postoperative gastritis are rather common after gastroenterostomy. More infrequently, recurrent ulceration has led to formation of a gastrojejunocolic fistula, usually after an interval of time has elapsed after operation. A complication which may not be thought of, and to which Smith and Rivers<sup>3</sup> call attention, is the presence of a gastroenteric stoma which is actually gastroileal instead of gastrojejunal. This low anastomosis is the result of a surgical error.

The symptoms of gastroileal stoma are dependent chiefly on the location of the anastomosis and on whether or not ulceration is present.

Diarrhea was present in six of the nine cases reported in this series of cases. In five of these, it began immediately or within a few days after operation. In the sixth case, a month elapsed before diarrhea appeared. The lenteric character of the stools was indistinguishable from that seen in cases of gastrojejuno-

colic fistula, but the latter would be unlikely as a cause of symptoms coming so soon after operation, a point which is of diagnostic value. Of the three other patients in the series, two with upper ileal anastomoses had had vomiting. One interesting feature is that with but one exception diarrhea occurred only in those cases in which the anastomosis was very close to the large bowel. In two of the cases in which anastomosis was very close to the cecum, fecal belching occurred. Diarrhea coming quickly after operation is the chief reason for suspecting a gastroileal stoma. Epidemic diarrhea or postoperative ulcerative colitis might be confusing but cultures of stools and proctoscopic examinations help to distinguish these when seen early. Later these can be excluded rather accurately on the basis of the patient's history.

Vomiting may be of retention type and occasionally has a fecal quality or is accompanied by a belch with fecal odor.

Loss of weight may be severe and usually can be attributed to loss of partially digested food in the lenteric stools before adequate absorption occurs.

Pain in association with gastroileostomy may be of bowel type or of ulcer type. The former is usually lower abdominal and of cramping type with relief on passage of flatus, stool, or an enema. The pain of ulcer type may be burning or cramping and may be referred to the umbilical region or lower abdominal quadrants in much the same fashion as is the pain of gastrojejunal ulcer. Ulcer sequence and neutralization relief are atypical, however. When pain as a symptom is present, the chances of finding a gastroileal ulcer or gastroileitis are good only when a significant amount of free hydrochloric acid is present on analysis of gastric contents.

Aside from the complications of gastroileitis and gastroileal ulcer, patients who have gastroileal stomas may be subject to nutritional deficiencies.

Diagnosis of gastroileostomy should be suspected if there is a history of onset of diarrhea very soon after gastroenterostomy. If the stools are lenteric and are accompanied by loss of weight, the possibility becomes strong. Vomiting and fecal belching may or may not be present. Roentgenological examination is of the greatest value in making the diagnosis.

If a gastroileal stoma is diagnosed and pain similar to that present with gastrojejunal ulcer exists, a gastroileal ulcer may be suspected. If the patient is a man, if he had an ulcer before his operation and now has free hydrochloric acid in greater concentration than 30 units after stimulation by a test meal, the chances are that either gastroileitis or frank gastroileal ulcer is present.

Treatment of gastroileostomy and gastroileal ulcer is surgical. The procedure used depends, of course, on satisfying the requirements of restoring adequate gastrointestinal continuity and of correcting the primary problem. Part of this may be accomplished by disconnection of the abnormal anastomosis and excision of any gastroileal ulcer. If the duodenum is normal, nothing further may be required. If the duodenum shows evidence of healed or active ulceration, gastrojejunostomy may be sufficient. However, if either duodenal or gastroileal ulcers are active and secretion of free hydrochloric acid by the stomach is significant, it may be wise for the surgeon to consider partial gastrectomy. The prophylactic value of this procedure must be weighed against the additional risk imposed, especially if the patient's general condition has been depleted by the gastroileostomy.

## Peptic Ulcers

**Bleeding Peptic Ulcers**—Postmortem study made by Blackford and Allen<sup>4</sup> in more than half (76) of 151 fatalities in Seattle hospitals record the location of the ulcer as gastric in 46 cases and duodenal in 26 cases; in four cases, the location is not recorded. Thirty-one women and 120 men died from bleeding ulcer, showing that one-fifth were women. Only one death occurred in the twenties, one in the thirties and six between the ages of 40 and 45 years. After the age of 45, there is a great increase in the number of deaths. Nearly two-thirds of all bleeding ulcer deaths occur in the fifties and sixties.

The authors found it a striking fact that in the majority of cases there was not a history of extremely severe ulcer. In a remarkable number, there had been really mild ulcer symptoms; many patients did not even know that they had peptic ulcer. One-third of the fatal hemorrhages occurred during a period of quiescence of any ulcer symptoms. In only 35 cases (23 per cent) was there a history of former hemorrhage; more than three-fourths of all fatalities occurred following the first hemorrhage.

**Perforated Peptic Ulcer**—Bacterial infection of the peritoneal cavity is a major cause of death in cases of perforation in a peptic ulcer. Henry's<sup>5</sup> observations indicate that there is almost as high a percentage of positive bacteriologic cultures in perforation under six hours as there is in those of longer duration.

**Results**—Harrison and Cooper<sup>6</sup> studied 57 cases of acute perforated peptic ulcer, 51 duodenal and 6 gastric, for the purpose of testing the validity of the widespread opinion that if a peptic ulcer perforates, and if the patient recovers after closure of the perforation, subsequent permanent healing of the

TABLE I  
BACTERIAL GROWTH IN PERITONEAL FLUID FROM  
PERFORATION UNDER AND OVER  
SIX HOURS OLD

	Growth	No Growth	Percent of Growth
Swab cultures from perforations under 6 hours old.	38	23	62
Swab cultures from perforations over 6 hours old.....	27	14	66

TABLE II  
BACTERIAL GROWTH FROM BOTH SWAB AND  
LARGER SPECIMENS OF PERITONEAL FLUID

	Total Cases	Growth	No Growth	Percent of Growth
Swab.....	48	31	17	65
3 cc.....	48	39	9	81

TABLE III  
INCIDENCE OF ORGANISMS IN 65 CULTURES OF  
PERITONEAL FLUID

Nonhemolytic streptococcus (including <i>Streptococcus viridans</i> ).....	55
Hemolytic streptococcus.....	1
Staphylococci.....	6
<i>Bacillus coli</i> .....	6
Miscellaneous.....	4

ulcer may be expected to occur. The operative procedure consisted in the removal of all available foreign material in the peritoneal cavity followed by simple closure of the perforation either by pursestring or Lembert sutures. The incidence of recurrence of symptoms of ulcer postoperatively, after simple closure of the perforation, was found to be 82.5 per cent. Following recovery from the operation for closure of a perforated peptic ulcer, the patient's condition should be evaluated anew and treatment should be the same as for any other case of peptic ulcer.

## DUODENUM

### Congenital Duodenal Obstruction

Chronic duodenal obstruction which results from a congenital anomaly is rare, particularly among adults. The causes of congenital duodenal obstruction are usually divided into intrinsic and extrinsic causes. Among the intrinsic causative factors are atresia of the lumen, formation of a septum, and complete absence or suppression of segments. Among the extrinsic factors are included abnormal fixation of the duodenum, persistence of the hepaticoduodenocolic ligament, annular pancreas and vascular anomalies. Prenatal mesenteric cysts, tumors or cysts of the liver and pancreas are also known to cause duodenal obstruction. It is common to find associated intra-abdominal anomalies in cases in which congenital duodenal obstruction exists. Malrotation of the intestine frequently results in chronic duodenal obstruction. Duodenal obstruction secondary to a congenital anomaly is usually manifest soon after birth. If the obstruction is complete, the condition is incompatible with life and unless it is recognized and relieved, death will occur in from 1 to 12 days. Reports of successful surgical relief of these obstructions in early life are appearing more frequently. With partial obstruction, life may be considerably prolonged and the patient may reach adulthood. It has been stated that regardless of how long the first appearance of symptoms is delayed, these infants do not attain the development of normal children. This statement must be modified by the knowledge that in certain cases of incomplete obstruction normal development may occur. This fact is demonstrated by Gray and Morlock.<sup>7</sup>

The symptoms of congenital occlusion depend largely on the degree of obstruction present. Vomiting always

occurs, and is severe and persistent if the obstruction is complete; it may be intermittent if the obstruction is incomplete. The vomitus may or may not contain bile; it usually contains undigested particles of food and occasionally

has been reported in cases in which the obstruction encroaches on the ampulla of Vater. Distress may or may not be experienced. When present, it varies from a dull to a severe colicky pain simulating such abdominal lesions as ap-

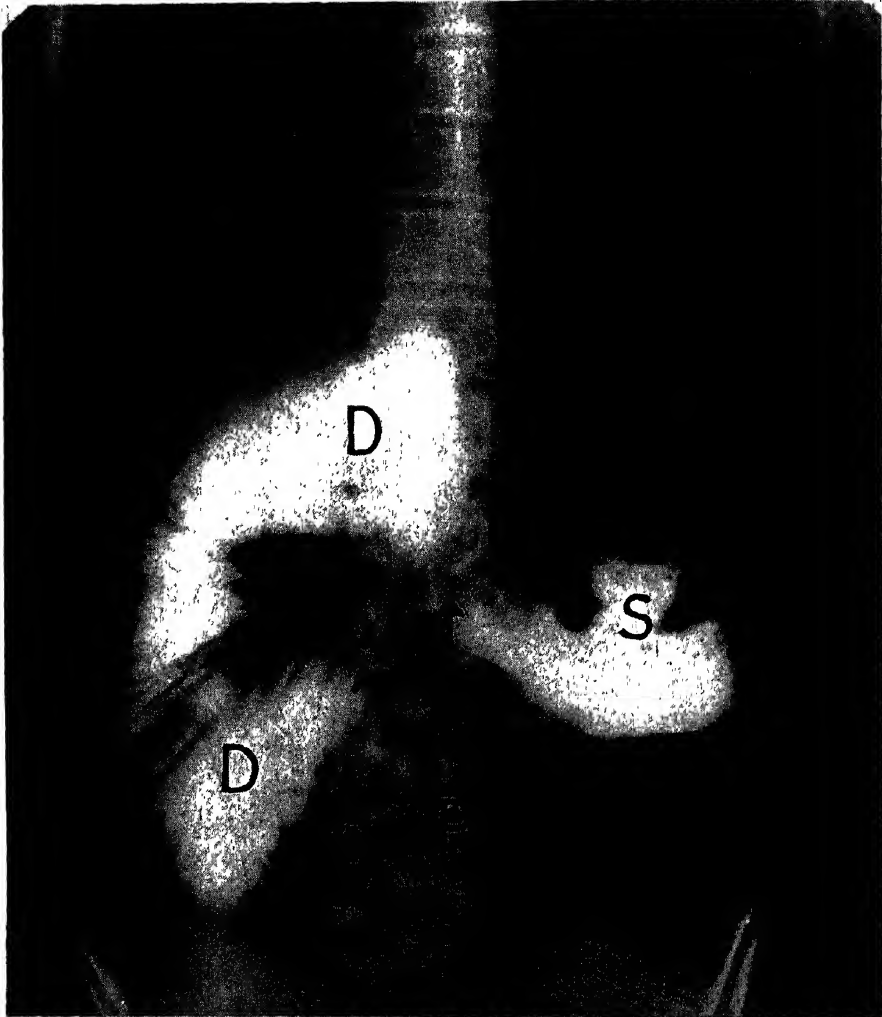


Fig. 1—Hugely distended duodenum (*D*). The pyloric canal (*P*) is widely dilated; the stomach (*S*) is dilated and atonic. (C. G. Morlock and H. K. Gray: *Ann. Surg.*)

fresh blood. If, as frequently occurs, enlargement of the duodenum becomes marked, distention involving the upper part of the abdomen, most particularly the right side, and an apparent retraction of the lower part of the abdomen are present. Uncommonly, peristaltic waves are visible and duodenal succussion sounds may be heard. Jaundice

pendicitis, duodenal ulcer, or acute biliary disease. When pain occurs, relief is often afforded by a change in posture or by pressure on the median line below the umbilicus.

#### Duodenal Diverticula

**Significance**—The three main theories<sup>8</sup> covering the origin of diverticu-



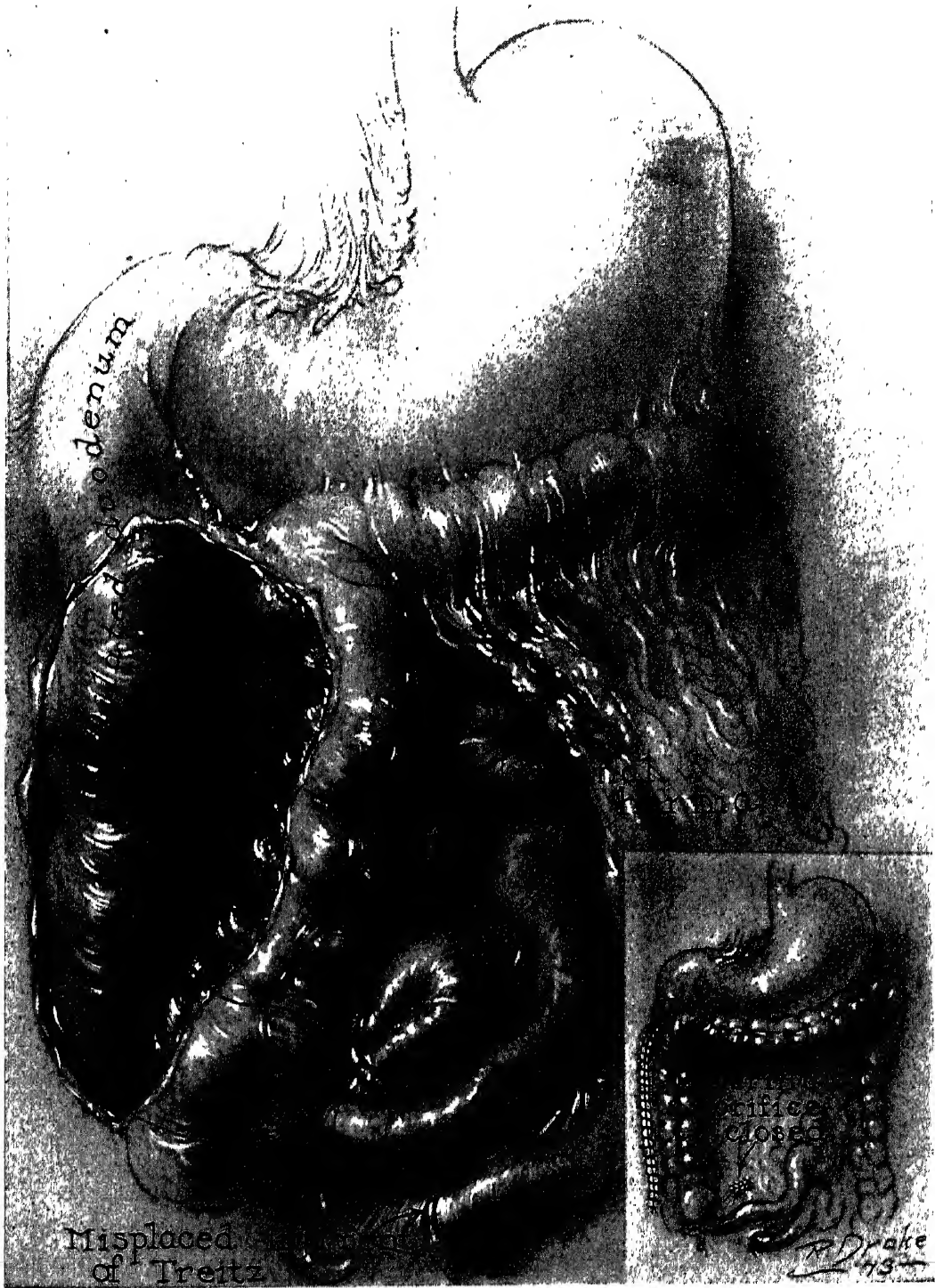


Fig. 2—The appearance of the abdominal viscera at exploration. The second and third portions of the duodenum have invaginated between the leaves of the ascending mesocolon. There is incomplete rotation of the colon. Obstruction of the duodenum has resulted from herniation of first portion of the jejunum through a defect in the mesentery of the ileum. *Insert:* The appearance of the abdominal viscera at the completion of the operation. (C. G. Morlock and H. K. Gray: Ann. Surg.)

losis and diverticulitis are traction, pulsion, and congenital or developmental weak spots. It seems probable that most acquired diverticula of the bowel result from a combination of pulsion and congenital weak spots, with the main emphasis on the latter. In the duodenum, the diverticula occur almost invariably on the outer or mesenteric border, in close association with the head of the pancreas, the entrance of its duct into the bowel, and the ampulla of Vater. By far, the greater number of diverticula occur in the second portion of the duodenum in intimate association with the head of the pancreas. They may at times seriously encroach on the common bile duct with resultant jaundice. In size they vary from  $\frac{1}{2}$  cm. to a hazlenut, occasionally being as large as a tangerine. The shape is globular ovoid with the wide mouth attachment toward the bowel. Most cases fall in the age decades between 50 and 70 years. From all the available figures, it seems probable that duodenal diverticula occur in between 1 and  $\frac{1}{2}$  per cent of adults. There are very few reports of perforation of duodenal diverticula, although a number of authors report evidence of acute or chronic inflammation.

Regarding the symptomatology of diverticula, the picture is rather hazy. Most all of them are accidental discoveries either by roentgenography, at operation, at autopsy, or at the dissecting table. They present, of themselves, no recognizable clinical picture. This results from the fact that they are relatively asymptomatic. Frequently duodenal diverticula are mixed up in symptomatology with associated gastric or duodenal ulcers, active or healed. The incidence of coexisting gallbladder disease is even higher, as judged from the literature. If the sac is buried in the pancreas, an associated pancreatitis may result. The

most constant symptomatology for duodenal diverticula is somewhat as follows: Discomfort comes in attacks, without periodicity or any particular cycle connected with the ingestion of food, and often with long periods of entire comfort between attacks. The pain is characterized as a marked fullness, not passing through to the back but remaining localized in the epigastrium. Rarely does it threaten life.

**Treatment**—Very few diverticula of the duodenum are of surgical significance. Finney has encountered 19 cases. Six patients were operated upon with two deaths. The sac may be dissected out and resected or internally obliterated.

## JEJUNUM AND ILEUM

### Nonmeckelian Diverticula of the Jejunum and Ileum

At the Mayo Clinic from 1909 to 1942, inclusive, diverticula of the small intestine, exclusive of duodenal and meckelian diverticula, were observed in 122 cases. Approximately 200 cases, aside from the Mayo Clinic cases, are recorded in the literature. Although these diverticula in the jejunum and ileum are not related to the embryonic omphalomesenteric duct, the work of some investigators has indicated that they may be of congenital origin. Others have presented a variety of evidence to show that these diverticula are, in the great majority of instances, of the acquired type. Nonmeckelian diverticula of the small intestine occur more frequently in the jejunum than they do in the ileum. These diverticula may occur in any position around the circumference of the bowel; however, the majority are situated along the mesentery. Sometimes they are actually within the mesentery, pushing the leaves of this structure apart. The diverticula vary in size from

a few millimeters in diameter to large outpouchings. The openings by which these diverticula communicate with the bowel vary from 1 mm. in diameter to large lumina 3 to 4 cm. in diameter. When these diverticula are large, their walls may be of tissue paper thinness. In such cases the wall consists merely of serosa and a very thin layer of mucosa. Small diverticula have thicker walls con-

common symptoms. These symptoms are in no sense characteristic of any disease and are, therefore, of little aid to the clinician in the diagnosis of this condition.

Diverticula of the small intestine give symptoms when complications occur.

Complications of, or associated with, nonmeckelian diverticula of the jejunum and ileum:



Fig. 3—Postmortem specimen obtained from a white male, age 62; dead of coronary thrombosis, showing multiple large and small diverticula on the mesenteric border of the jejunum. (R. E. Denson, C. F. Dixon, and J. M. Waugh: *Ann. Surg.*)

sisting of the usual intestinal structures.

Nonmeckelian diverticula of the jejunum and ileum are noted in all age groups. The youngest in this series<sup>9</sup> of patients was 12 years, the oldest 91 years of age. Approximately two-thirds of diverticula of the small intestine occurred in the male sex. These diverticula are not easily identified at the operating table. Even when they are distended with intestinal contents, they may offer so little resistance to the palpating hand that they will escape identification. Often they are hidden in the leaves of the mesentery. According to Weber, the roentgenologist can diagnose the condition with comparative ease by roentgenoscopic and roentgenographic examination.

Uncomplicated diverticulosis of the small intestine does not give rise to any characteristic symptoms. Abdominal discomfort and flatulence are the most

*A. Acute mechanical intestinal obstruction:*

1. From enteroliths formed within diverticula.
2. From pressure of inflammatory mass associated with diverticulitis.
3. From volvulus of the intestine.
4. From stricture or adhesions from ancient diverticulitis.
5. From pressure of filled diverticula on intestine.

*B. Chronic intestinal obstruction:*

1. Without apparent mechanical obstruction.
2. From stricture or adhesions.

*C. Inflammatory disturbances varying from mild catarrhal inflammation to gangrene resulting in perforation and peritonitis.*

*D. Intestinal hemorrhage.*

*E. Rupture of diverticulum:*

1. Spontaneous.
2. Traumatic.

*F. Foreign bodies:*

1. Bones, etc.
2. Parasites.
3. Enteroliths.

*G. Neoplastic disease and formation of heterotopic tissue:*

1. Benign:
  - (a) Fibroma.
  - (b) Lipoma.
  - (c) Accessory pancreatic tissue.
2. Malignant:
  - (a) Carcinoma.
  - (b) Sarcoma.

Uncomplicated and asymptomatic diverticulosis of the jejunum or ileum does not require surgical treatment. When acute complications, such as intestinal obstruction, diverticulitis or rupture of a diverticulum present themselves, sur-



Fig. 4—Diverticulosis and chronic obstruction of the jejunum 145 cm. in length, consisting of a portion of duodenum and proximal jejunum. The bowel is markedly dilated and hypertrophied. Many thin-walled diverticula are present on the mesenteric border. No mechanically obstructing lesion was observed. (R. E. Benson, C. F. Dixon, and J. M. Waugh: *Ann. Surg.*)

Spontaneous perforation of a diverticulum of the jejunum or ileum may occur. In these there is sudden, severe abdominal pain followed by the signs and symptoms of rapidly spreading peritonitis. Death ensues quickly unless the surgeon intervenes and closes the perforation.

Surgical treatment is often imperative. In operations upon such cases, it is probably best to limit surgical treatment to relief of the urgent condition. An attempt at surgical elimination of the diverticula is justified when persistent distressing symptoms, the syndrome of diverticulosis and chronic obstruction, or other chronic

complications are present. As a rule, enteroenterostomy, sidetracking the involved segment, is preferable to resection, and anastomosis in one stage unless the diverticula are localized to a small segment. These patients are often poor

involved segment may be resected with less risk at a later date.

### Carcinoid Tumors of the Ileum

Carcinoid tumors involving the ileum produce clinical evidence of obstruction

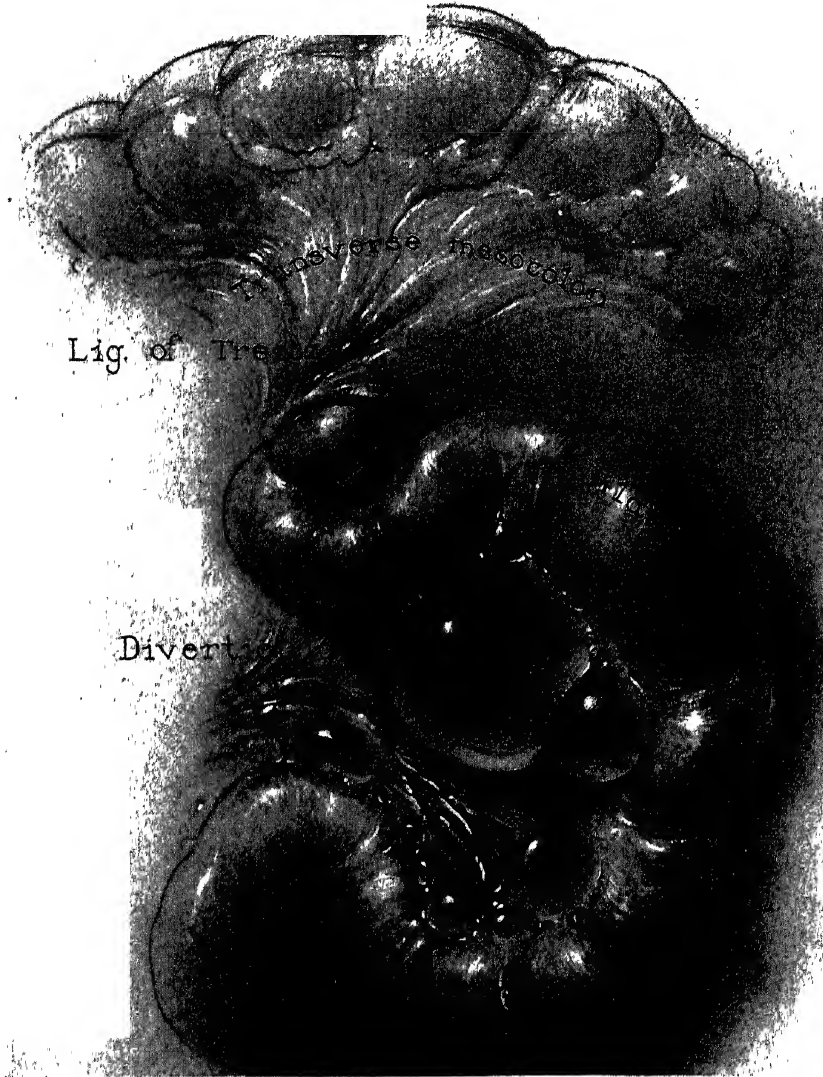


Fig. 5—Diverticulosis and chronic obstruction of the small intestine, showing dilation and thickening of the intestinal wall. Multiple diverticula are present on the mesenteric aspect. Obstruction resulted from adhesive bands. (R. E. Benson, C. F. Dixon, and J. M. Waugh: *Ann. Surg.*)

surgical risks. There is also a distinct danger of rupturing one of the fragile, thin-walled diverticula during an extensive operative procedure. A short circuiting procedure alone may relieve the patient of his symptoms. If not, the

in about one-third of the cases, and small tumors thus located may produce major disturbances. About 25 per cent appear as multiple nodules.

**Symptoms**—Symptoms referable to disturbed intestinal function had been

present in 9 of the 13 cases reported by Dockerty and Ashburn<sup>10</sup> for an average duration of 42 months. A history suggestive of chronic, slowly progressive, intestinal obstruction was elicited from eight patients. These obstructive symptoms were usually mild, and the patients, on examination, appeared relatively well nourished. Obstructive features in these eight cases often were described as episodic with crampy abdominal pain coming on in attacks, sometimes related to ingestion of food and occasionally relieved by regurgitation. Distention accompanied these attacks, which recurred with increasing frequency. Constipation was present in three cases, moderate to severe diarrhea in two, and mild looseness in one. In six cases, one or more abdominal masses were clinically palpable. These masses were variously located, were semifixed, did not move with respiration, and were not tender or were only slightly tender. Recently Miller and Herrmann described a roentgenologic sign which enabled them in one instance to arrive at the correct preoperative diagnosis of ileal carcinoid tumor. Acute buckling or kinking of the bowel is a common finding in cases in which carcinoid tumors have infiltrated the serosa.

**Treatment**—In 3 of the 11 cases in which operation was performed, the operation was confined to *exploration with biopsy*, because of widespread intra-abdominal metastasis and fixation of coils of intestine. In one case, in addition to the aforementioned procedure *ileocolostomy* was possible with short-circuiting of the growth. In five of the seven remaining cases, *one-stage resection* was effected even though three patients had hepatic metastasis. In two cases, *operative removal in two stages* was dictated by the general condition of the patient. Evidence has been

afforded that in the case of carcinoid tumors growth of metastatic deposits may become stationary following removal of the primary tumor.

**Prognosis**—The life history of carcinoid tumors is one of slow evolution, with a long preoperative phase and with surprisingly long postoperative survival of patients so afflicted. Among the 11 cases in the present series in which operation was performed, one patient died several days after biopsy for an inoperable tumor, two patients succumbed two and five years after operation respectively, apparently as a result of local recurrence and metastasis, but the remaining eight patients were living and surprisingly well for periods varying from 10 months to 19 years, even though several had hepatic metastasis.

## LARGE INTESTINE

### Operative Treatment of Cancer of the Large Bowel Without Colostomy

Over 60 per cent of cancers of the large bowel may be accurately and instantly diagnosed by palpation with the finger or by inspection through a proctoscope. Commonly a roentgen examination is ordered, which usually fails to delineate a cancer of the pelvic colon.

In discussing particularly the morbidity of operations for malignancy of the large bowel, Babcock and Bacon<sup>11</sup> found the greatest mental distress and physical discomfort that follow the operation are due to *colostomy*. Recent mortality statistics from various clinics where colostomy is an essential part of the operation, although not entirely comparable, suggest that the colostomy does not add to the safety of the operation. Since 1930, when Babcock began to eliminate routinely establishment of a permanent abdominal colostomy opening in operating for removable cancer of the large bowel, he had had 367 opera-



tions for this condition on patients from 23 to 88 years of age; 208 were single stage resections for carcinoma of the rectosigmoid or anus. These include 99 *abdominoperineal proctosigmoidectomies*, 99 *perineal proctectomies* or *proctosigmoidectomies* and 9 *resections with primary end-to-end anastomosis*. Of the 208 patients, 24 died in the hospital, a mortality of 11.6 per cent. In 1939 technical improvements came into routine use, including improvements in anesthesia, use of non-irritating suction, or of dependent drains and modifications to insure a more functional anal opening; 161 patients have had operations for cancer of the large bowel since 1939, with 11 deaths in the hospital, or a mortality of 6.8 per cent.

In 12 patients, there was no special difficulty in moving to the perineum the opening left after a Miles operation or some other procedure.

Is the perineal opening, even without sphincter control, worth while? From 11 patients, Babcock has learned that the discharge of offensive gas is much less evident from a perineal opening. The perineal opening is more convenient and easier to care for and evacuations are more satisfactory and less frequent. Each of the 11 patients considered the transplantation of the fistula to the perineum of great advantage.

Five to 10 per cent of patients with a perineal colostomy opening without sphincter control require no local protection or change in diet except during periods of diarrhea. To limit soiling, about 85 per cent require an emptying of the colon by an enema or a quickly acting laxative every third or fourth day. By this expedient the majority dispense with the use of a protective pad most or part of the time.

However, with over 85 per cent of cancers of the large bowel, the pelvic floor is not involved, and a functional anus with its sphincters may be retained safely instead of being sacrificed, as in the conventional operations now used. Many observations indicate that the lymphatic extension of cancer of the rectosigmoid is cephalad, not caudad. While a wide removal of intestinal and lymphatic tissue is imperative on a level with and proximal to the growth, a much less extensive resection below the tumor is required. Therefore, with a rectal cancer 7 cm. or more above the pelvic floor, the anus and functional sphincters may be retained.

In any case, the abdominal liberation of bowel, mesentery, and lymphatics resemble that of the Miles operation, except that a left oblique inguinal incision usually is employed. To reduce the bulk of tissue to be delivered through the perineum and to afford space for the formation of a pelvic diaphragm, the liberated bowel may be divided by cautery between double clamps of the deMartel type and removed. With cancers low in the pelvis, this is not feasible, and there is tied about the loop of freed bowel at the level to be used for the perineal anus a folded gauze tape, the ends of which are packed against the floor of the pelvis before the abdomen is closed. It is essential that sufficient vascular sigmoid be liberated (five inches) to reach from the posterior pelvic brim through the perineum. Viability is determined by observing pulsating arteries or by the character of bleeding when the small vessels on the surface of the bowel are incised. If necessary, the descending colon is slid to a lower position, after its lateral peritoneal leaflet has been divided. If the bowel is resected between clamps through an abdominal incision, the proximal and distal ends are en-



cased in stockinet tubing and placed on the floor of the pelvis, a pelvic diaphragm is formed, and the abdomen is closed. With the patient in lithotomy position, an anterior perineal delivery of the ends of the bowel through an incision of the Young prostatic type gives a better anal opening, since the bulk of the anal muscles lies posterior to the anus. This incision also facilitates the resection of an invaded prostate. Through the opening anterior to the anus, the stockinet ends are grasped and used to deliver the ends of rectum and sigmoid. The lower end of the rectum is divided by cautery just above the sphincters. A Payr clamp is passed through the anus and caused to grasp the sigmoid above its clamp, which is burned off by cautery. The Payr clamp and end of the sigmoid are withdrawn through the anus,

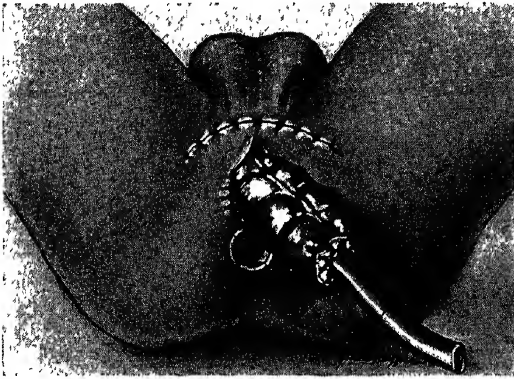


Fig. 6—The rectum and part of the sigmoid have been liberated and resected between short clamps through an abdominal incision and the clamped ends have been delivered and further resected through an anterior curved perineal incision. The sigmoid end has been brought through the anus, which has been split anteriorly, and a rectal tube has been tied in. A perforated curved glass drain is inserted along the sacrum through a stab wound at the right side of the coccyx. (W. W. Babcock and H. E. Bacon: Arch. Surg.)

and the perineal incision is closed with interrupted layer sutures of fine alloy steel wire. Through a median stab wound near the tip of the coccyx, a curved, perforated glass sacral drain is

inserted. If the rectum is attached posteriorly, a median cutaneous incision is made from the posterior border of the closed anus and deepened along the side of the coccyx into the pelvic cavity. The

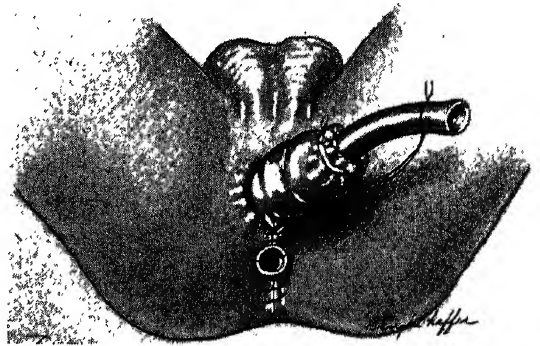


Fig. 7—The loop of cancerous rectum and sigmoid liberated through the abdomen has been delivered through a midline posterior anal perineal incision. This loop of bowel has been divided through the sigmoid and was just above the sphincters. The sigmoid has been placed in the gutter formed by the split anus and a rectal tube has been tied in. (W. W. Babcock and H. E. Bacon: Arch. Surg.)

stockinet covering the clamped ends of the bowel is then grasped, the bowel is liberated and the ends are pulled through the perineum. The aseptized rectal end is divided by cautery just above the sphincters, the anus is split posteriorly and the end of the sigmoid laid in the anal groove. A perforated curved glass drain is inserted along the sacrum, to be removed after 24 hours, and the perineal wound is partly closed with buried and superficial sutures of 32 B. & S. gage alloy steel wire.

A variation of the operation is to pull through the perineum the unopened loop of rectosigmoid by a tape previously tied about the sigmoid at the level where the new anus will be formed. The posterior incision leaves an anus of keyhole shape which in two months or more may be improved, if desired, by turning forward a U-shaped flap formed externally along the posterior cutaneous margins of the exposed sigmoid. The sphincters, peri-

neal muscles and skin are united under the flap with interrupted wire sutures. If an anterior spur has formed where the sigmoid joins the anus, this should be split anteriorly and sutured before the U-shaped flap of bowel is raised. Except when a plastic operation is performed a rectal tube is tied in the protruding sigmoid, which should not be sutured to the perineum. A week later, when adhesions have formed, the pro-

there is danger of pelvic infection, and a retracted and cicatricial bowel opening often forms.

The preservation of the sphincters is more difficult with the perineal resection and, of course, is not to be attempted for a low-lying cancer. Babcock has preserved functional sphincters by using a long medial perineal incision to expose the rectum just above the sphincters, the rectum being divided be-

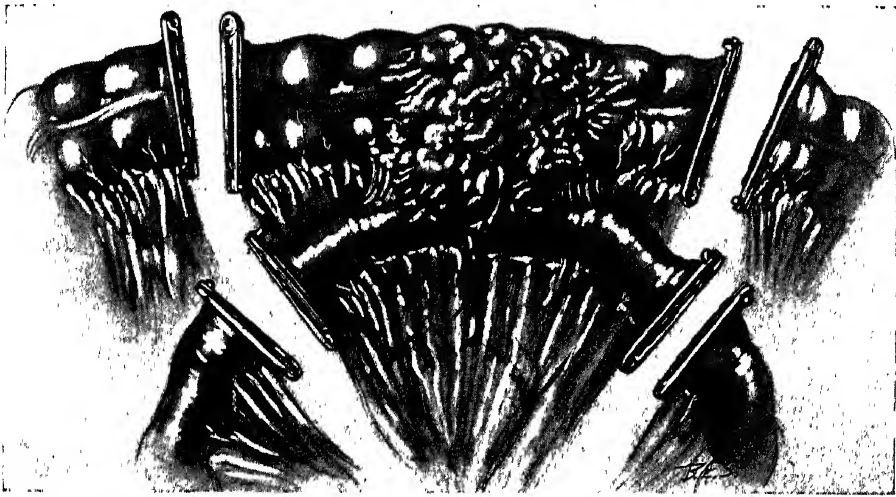


Fig. 8—Use of 8 short clamps as in a combined aseptic resection of colon and jejunum for infiltrating carcinoma or jejunocolic fistula. The clamps have been applied and the segments divided by cauterization. (W. W. Babcock and H. E. Bacon: *Ann Surg.*)

truding insensitive end of the sigmoid is burned off by cauterization. The patient is out of bed by the sixth day and in condition to leave the hospital by the twelfth or fourteenth day.

For low-lying anal and rectal cancers, a wide excision of the pelvic floor is made, and the withdrawn sigmoid is placed in the position of the anus. Such a perineal or posterior resection is a useful operation for the aged and very obese and for some patients with involvement of the vagina and prostate. It has the great disadvantage that it is difficult after any extensive perineal rectosigmoid resection to bring the divided end of the bowel to the perineum without interfering with its blood supply. As a result

tween ligatures. The first incision is then completed vertically through the anus, the margins retracted, and the rectosigmoid widely liberated and delivered through the split anus. This procedure is followed by reconstruction of the perineum with drainage. In all these operations, a preliminary careful cleansing and packing of the rectum with antiseptic gauze is employed.

A secondary perineal hernia, for which a plastic operation may be done if the condition is annoying, develops after excision of the pelvic floor in about 5 per cent of perineal excisions.

A moist opening from mucous prolapse may be corrected by linear cauterization, which may be done nearly

painlessly as an office procedure. If there is a tendency to contraction of the new opening, the patient is given a set of test tubes to be used as dilators.

For resections of the colon above the pelvis, the present tendency is toward *resection with end-to-end anastomo-*

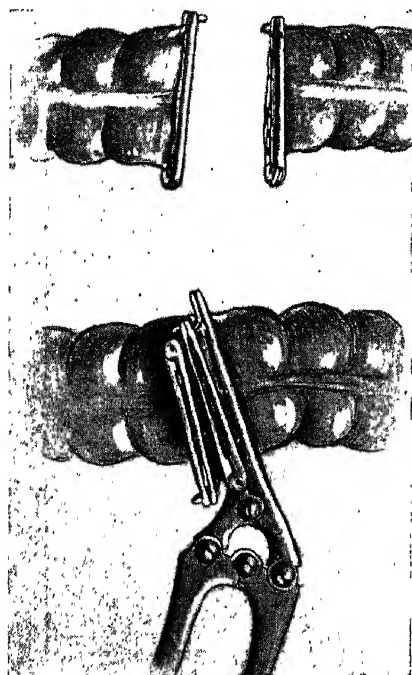


Fig. 9—Method of end-to-end anastomosis over a single clamp after the diseased adherent segment shown in Fig. 4 has been removed. The clamped ends of bowel are aligned and clamped together by an underlying Payr clamp, and the ends are burned off by cautery. This leaves the ends of the bowel in the grasp of the single Payr clamp in position for an aseptic end-to-end suture. (W. W. Babcock and H. E. Bacon: Ann. Surg.)

*sis* and *complemental appendicostomy or enterostomy* well proximal to the anastomosis. With the development of nonirritating suction drains for the peritoneum and a satisfactory one clamp method of end-to-end anastomosis with fine alloy steel wire sutures, the mortality subsequent to the anastomosis now compares favorably in Babcock's experience with that associated with the Paul-Mikulicz exteriorization procedure, while the morbidity is much less. Probably it is a little more dangerous for

resection of the sigmoid and rectosigmoid, but it surely seems safer for the right and transverse portions of the colon, where a modified Mikulicz procedure has given a mortality of 16.6 per cent in expert hands. With the Mikulicz operation, as with any colostomy, there are a certain number of deaths from spreading pyoderma and other complications, and often even when a muscle-splitting incision is used, a weak area is left in the abdominal wall.

The lowest mortalities from resection of the colon in recent years have been reported by operators who have become adept in a single stage operation.

A four-clamp method facilitates the removal of the ileum, uterus, or other organ to which the cancerous colon has become attached. Two light clamps are applied on each side of the bowel lateral to the growth, and the colon is divided by cautery between each pair of clamps. This leaves the diseased intestinal segment attached to the uterus or other organ, which is then removed or resected. The distal and proximal clamps are now apposed over a single Payr clamp and burned off. The end-to-end aseptic suture is then completed over the single clamp.

When the cancer has invaded an adjacent loop of small intestine, it usually is feasible to fold the intestinal loop together and then apply two Payr or deMartel clamps obliquely across the base of the loop, which is divided by cautery between the two clamps. A similar operation may be used when a cancer of the transverse colon has invaded the stomach. Again, adhesions or other condition may render an eight-clamp double resection desirable. Here the small and the large intestine are resected, each with four clamps.

In resections of the colon above the sigmoid, including the ileocecum, for a

number of years an end-to-end anastomosis only was used. By apposing an oblique section of the smaller ileum to a transverse section of colon, a satisfactory end-to-end union may be made.

When the cancer has invaded the anterior abdominal wall, this may be re-

with large surfaces which cannot be re-peritonealized or covered with omentum after extensive dissections of adherent masses. In regional enteritis, for example, he may be forced to resect a fixed mass involving several feet of small intestine and perhaps a portion of the

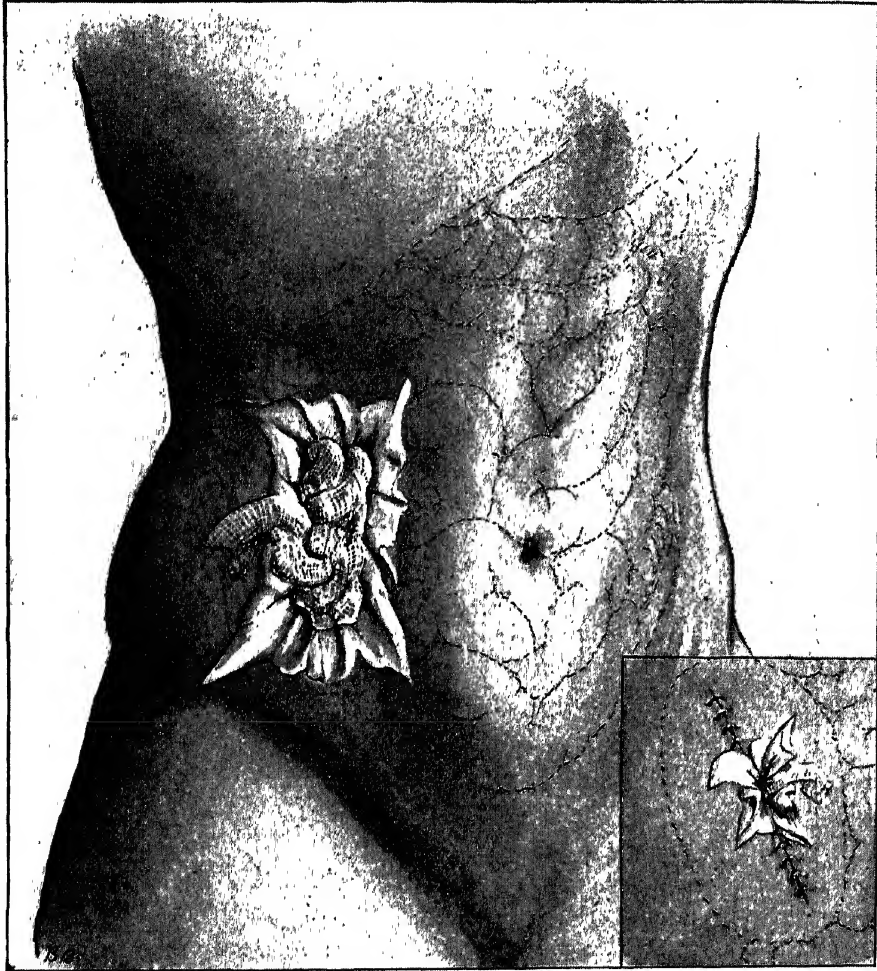


Fig. 10—Diagrammatic sketch of pack after closure. (T. E. Jones, J. R. Paxton, and R. E. Brubaker: *Ann. Surg.*)

sected *en bloc* with the disease segment of bowel. Even when the colon has perforated into the abdominal wall with the formation of a localized abscess, the *en bloc* resection should be used if possible.

#### The Intra-abdominal Use of the Mikulicz Pack

The abdominal surgeon is frequently confronted with the problem of dealing

ascending colon, rendering the entire right lower abdomen a raw, oozing surface. After mobilization of a large neoplasm of the sigmoid, the major portion of the pelvic basin may be denuded of peritoneum. Jones<sup>12</sup> *et al.* have been impressed in these and similar instances with the value of the mechanical exclusion of the small intestines from contact with such areas. If loops of small bowel

are allowed to prolapse into a freshly denuded intra-abdominal basin, some degree of obstruction frequently occurs, due to adherence and kinking. In addition, if such an area is infected or contaminated, at least a localized peritonitis will result. The abdomen can withstand peritoneal infection to a marked degree, but

area to be covered: (1) A large square sheet of rubber dam is placed against an unperitonealized area and packed with a long gauze fold until the cavity formed by the removal of a mass is filled with the bulk of the pack (Fig. 10). The four edges of the rubber dam square are then gathered together and are brought



Fig. 11—Diagrammatic sketch of pack intra-abdominally. (T. E. Jones, J. R. Paxton, and R. E. Brubaker: *Ann. Surg.*)

the combination of infection and obstruction may frequently be fatal. A mechanical barrier which will cover the unperitonealized surface and fill the space from which a mass has been removed will prevent such an occurrence.

**Technic**—For many years Jones has used a modification of the Mikulicz pack, employing a sheet of rubber dam into which a large fold of gauze is packed. This may be applied in two ways, depending upon the size and shape of the

out of the abdominal wound together with inner gauze fold (Fig. 10a). The pack assumes a saclike shape with the neck at the abdominal wall (Fig. 11). One need not be concerned about the formation of a large intra-abdominal cavity with a relatively narrow opening, since it collapses rapidly within a few days after the entire pack is removed. (2) In the case of a deep narrow unperitonealized area, one edge of a rectangular piece of rubber dam is placed into

the bottom of the area and folded over gauze packing, forming in appearance a large cigaret drain.

In each case the inner gauze packing is removed gradually beginning the third or fourth postoperative day. The last portion of the pack and the rubber dam are usually removed between the eighth and eleventh postoperative day. A large rubber tube or catheter is placed into the cavity formed by the pack, and irrigations are carried out as often as necessary until it closes. With careful postoperative attention, such cavities assume the shape of vertical sinuses within a week, and the wounds are entirely healed in six to ten weeks.

**Uses**—The authors have found this type of pack of greatest value in two groups of cases: First, regional enteritis, especially those cases with enterocutaneous fistulae; and second, neoplasms of the sigmoid colon and the splenic and hepatic flexures. In regional enteritis with fistula formation, one nearly always finds at operation a densely adherent mass formed by loops of small intestine and often by the ascending colon. Extensive mobilization is necessary, leaving a large raw surface in the right lower abdomen. Furthermore, some degree of contamination is almost unavoidable in the dissection of the sinus tracts. In these cases they believe that the use of the modified Mikulicz pack leads to a smooth convalescence and frequently prevents a mortality which otherwise might be expected.

Neoplasms of the splenic flexure are the bane of surgery of the colon. Mobilization of the lesion is frequently difficult, and a wide area of peritoneum is denuded high in the upper left colonic gutter. It is hazardous to allow the small intestines to prolapse into the cavity formed by the dissection. In such instances, where reperitonealization is im-

possible, a Mikulicz pack is used routinely to fill this space. The pack is brought out through a stab incision in the left flank. With neoplasms of the hepatic flexure, the same situation frequently exists. Large, bulky, adherent carcinomata of the sigmoid colon often present difficulties. Frequently, they are surrounded by marked pericolic inflammation and abscesses. Mikulicz pack is the answer to the problem of handling the denuded and infected surface. The modified Mikulicz pack accomplishes several things simultaneously: First, it serves as a framework for the immediate formation of a protective wall of granulating tissue. It has the effect of limiting the spread of infection from a given area by establishing a counter-reaction in which the surrounding viscera adhere and seal off the general peritoneal cavity. Second, it prevents the contact of the small intestines with an unperitonealized surface during the period in which the peritoneum is reacting to the trauma of mobilization and combating the infection. Third, the pack acts as a drain. During first few postoperative days, large quantities of serosanguinous fluid saturate dressings.

No hernias of the abdominal wound have been observed at the point of exit of the pack. This, the authors attribute to the use of Babcock's alloy steel wire in wound closure.

### Intussusception

**Relation of Acute Intussusception of Childhood to Mesenteric Lymphadenitis**—Intussusception may be divided into two groups. The first group comprises those cases in which there exists a definite causative agent, such as an intraluminal or extraluminal tumor, anatomical anomalies, or Meckel's diverticulum. The second group is composed of those cases in which there is no demonstrable cause.



The term "acute intussusception of childhood" is limited to that type of intussusception appearing during the first two years of life, and most frequently between the third and eleventh month. In a high percentage of these children,

the patients. Perrin and Lindsay have shown that in children under two years of age, the ileocecal valve is relatively longer than in adult life and it, as well as the terminal four to six inches of the ileum, is studded with masses of lymph-

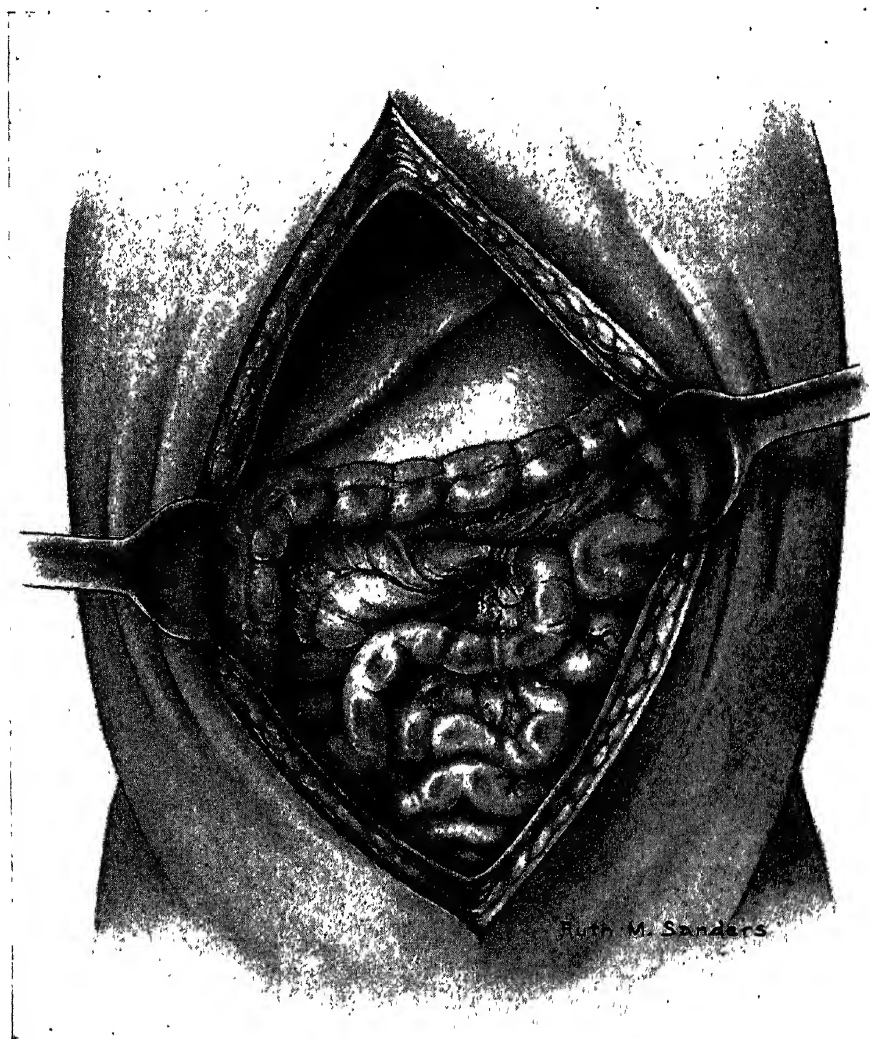


Fig. 12—Case 1. Stenosis of the duodenum near duodenojejunal junction. Findings in Case 6 identical. (J. W. Duckett: *Ann. Surg.*)

mesenteric lymphadenitis of the type Wilensky terms "nonspecific mesenteric lymphadenitis" is an associated pathological finding at operation.

In a recent study of 16 consecutive cases of acute intussusception of childhood, as seen by Avent,<sup>13</sup> mesenteric lymphadenitis occurred as an associated disease in seven, or 43.75 per cent, of

oid tissue which completely surround the lumen of the gut. They believe that the swelling of the pre-existing lymphoid tissue acts like a foreign body within the intestine to bring about the intussusception. The anatomical and age distribution of the lymphoid tissue in the alimentary canal agrees exactly with the anatomical and age distribution of all



primary intussusceptions. Almost all of the acute intussusceptions of childhood are ileocecal, a fact which again lends credence to the importance of lymphoid hyperplasia as its cause. It has frequently been observed that extraluminal

ently soon after birth. The vomitus is usually bile stained. It quickly becomes projectile, and everything taken by mouth is promptly lost if the obstruction is complete or almost so. The site of the obstruction cannot be predicted by the



Fig. 13—Case 2. Atresia of the jejunum and abnormal attachment at ascending and transverse colon. (J. W. Duckett: *Ann. Surg.*)

tumors adherent to the wall of the bowel may act as an intraluminal tumor does in precipitating an intussusception.

### Intestinal Obstruction in the Newborn

Congenital obstruction of the intestine should be suspected whenever a newborn baby begins vomiting persist-

time interval between birth and the onset of vomiting, since the entire intestinal tract above the obstruction is already distended at birth by digestive juices and swallowed amniotic fluid. When air and fluids are swallowed in the first feeding efforts, distention is further increased and vomiting results. When obstruction is incomplete or inter-

mittent, vomiting may begin later and may be less persistent, which makes diagnosis more difficult.

Anatomically considered, congenital obstruction may be intrinsic or extrinsic. The intrinsic obstruction is more frequent and may occur at any location.

threads. The condition is known as atresia when the bowel lumen is completely obstructed or when there is loss of continuity, and as stenosis when a small but ineffective opening is present. In either group, the clinical picture is essentially the same, although in steno-



Fig. 14—Case 4. Atresia and aplasia of the jejunum. (J. W. Duckett: *Ann. Surg.*)

It results from failure of re-establishment of the bowel lumen during the early weeks of fetal development. Proliferation of epithelium obliterates the lumen of the primitive gut for a time, but normally the lumen reappears after confluent vacuolization of the central mass. If this process is incomplete, one or more septa may remain to block the lumen, or sections of the intestine may be represented by fibrous cords or

sis the abnormalities are more likely to be amenable to surgical treatment. Extrinsic obstruction usually is a result of incomplete rotation of the colon associated with abnormally placed folds or bands of peritoneum which most frequently impinge upon the lower half of the duodenum.

The diagnosis of congenital atresia or stenosis can be made on the history alone. In the absence of intracranial

birth injury or unusual infection, bile-stained projectile vomiting beginning soon after birth and persisting almost invariably means obstruction of the intestine. Hypertrophic pyloric stenosis can be differentiated by the later onset

very poorly tolerated. Close co-ordination of medical and surgical care is an essential factor in survival. There is often jaundice with a consequent bleeding tendency, which must be combated with *vitamin K*. Treatment of meta-



Fig. 15—Case 4. Atresia of jejunum and aplasia of ileum. Abnormal attachment of ascending and transverse colon. (J. W. Duckett: *Ann. Surg.*)

of vomiting and absence of bile from the vomitus.

Survival of infants with complete obstruction depends on *early diagnosis and immediate repair* of the defect. Without surgery, death invariably occurs within a week or ten days in cases in which the obstruction is complete, and high degrees of partial obstruction are

holic disturbances, especially dehydration, requires *preoperative administration of fluids and blood transfusion*. Duckett<sup>14</sup> prefers ether anesthesia. In cases of intrinsic obstruction, the best chance of a favorable outcome is offered by the performance of a *primary anastomosis* about the site or sites of obstruction. Two stage procedures are

poorly tolerated. In extrinsic obstruction, Ladd has demonstrated that the most satisfactory results are to be obtained by releasing the peritoneal band lying across the duodenum and reducing the volvulus of the small intestine which

serosa-enclosed fat found along the colon from the cecum to the lower portion of the sigmoid, attached chiefly along the anterior taenia coli. Their size varies from a few millimeters to several centimeters. They often produce symptoms



Fig. 16—Case 5. Malrotation of colon; duodenal obstruction by band; volvulus of small intestine. (J. W. Duckett: Ann. Surg.)

is often associated with this lesion. He is impressed with the beneficial effect of *concentrated blood plasma* in the postoperative treatment.

#### Abnormalities

**Epiploic Appendages**—Epiploic appendages<sup>15</sup> are flattened projections of

closely simulating abdominal conditions requiring operation. Insidious in character, diseased epiploic appendages can produce symptoms which simulate appendicitis, cholecystic disease, intestinal obstruction, and other abdominal conditions. Epiploic appendages undergo the

following pathologic conditions: Torsion; infarction; thrombosis; cystic, hyaline, or calcareous degeneration; simple necrosis; gangrene; inflammation; hyperplasia and secondary carcinomatous implantation. Although simple necrosis of the pedicle may allow a tag to detach and not cause further trouble, the presence of infection in the diseased epiploic tag by organisms derived from contiguous bowel or some other structure may lead to peritonitis or localized reaction sufficient to cause obstructing lesions. The typical picture following acute torsion is considered to consist of moderate localized pain and tenderness in the abdomen of a rather obese young patient. There is little generalized reaction; the epigastric component of appendicitis and identifying criteria of other pathologic processes are absent. The temperature may be elevated and the leukocytes increased. Nausea, vomiting, and abdominal masses or signs of obstruction may be encountered.

## MESENTERY

### Arterial and Venous Mesenteric Occlusion

Analysis of 44 cases of portal and mesenteric occlusion by Laufman and Scheinberg<sup>16</sup> is shown in Table IV.

In no case of arterial occlusion which came to autopsy was the superior mesenteric artery spared; it invariably contained a thrombus.

The length of intestine involved by infarction or gangrene varied from 8 cm. to the length of the entire small intestine and half the large intestine in the proved cases.

**Etiology** — Warren and Eberhard have presented the following outline of the etiology of mesenteric vascular occlusion:

1. Known infection, including thrombophlebitis, appendicitis, pelvic abscesses, peritonitis, and general sepsis.

2. Hematogenous causation: Blood dyscrasias or changes known to predis-

TABLE IV

ARTERIAL OCCLUSION		VENOUS OCCLUSION	
Vessel:	*	Vessel:	
Superior mesenteric alone.....	9	Superior mesenteric alone.....	8
Superior mesenteric and inferior mesenteric.....	2	Superior mesenteric and inferior mesenteric.....	1
		Superior mesenteric and portal.....	6
		Portal alone.....	15
		Smaller mesenteric veins alone.....	3
	11		33

PORTION OF INTESTINE INFARCTED

Jejunum.....	3	Jejunum.....	3
Jejunum and ileum.....	6	Jejunum and ileum.....	6
Ileum.....	0	Ileum.....	2
Entire small intestine and ascending colon..	2	Entire small intestine and ascending colon..	2
	11	Intestine not involved.....	20
			33

TABLE V  
SUMMARY OF CAUSES OF MESENTERIC OCCLUSION

Cause	Arterial With Infarction	Venous With Infarction	Venous Without Infarction	Total
Abdominal operation.....	4	3	8	15
Heart disease.....	4	3	0	7
Arteriosclerosis.....	3	0	0	3
Liver disease.....	0	1	1	2
Malignancy.....	0	2	5	7
Abdominal infections.....	0	1	2	3
Splenic anemia.....	0	0	2	2
Congenital anomalies .....	0	2	2	4
Unknown.....	0	1	0	1
Totals.....	11	13	20	44

pose to thrombosis, such as splenic anemia and polycythemia vera.

3. Traumatic: Trauma of any sort to mesenteric vessels, tearing of mesentery and trauma from abdominal operations.

4. Mechanical: Largest group. Portal stasis, pressure from tumors, pressure from adhesions or congenital bands. Volvulus, strangulated hernias not included.

In two cases death from mesenteric arterial occlusion followed ablation of the lumbar sympathetic chain.

Table V lists the immediate etiological factors found in this series of cases. The predominating cause in younger patients was found to be heart disease or infection, whereas in older patients the degenerative or malignant changes appeared to be most important.

Of especial interest are those cases of portal or mesenteric venous occlusion which did not result in infarction of the intestine. Death in these cases was due to such factors as generalized sepsis, generalized thrombosis, toxemia or liver insufficiency. One case was that of a ten-day-old male infant whose mother developed puerperal sepsis. The infant had acute oomphalitis with thrombosis of the umbilical, portal, and splenic veins,

and died of peritonitis and sepsis. Another case was that of a 35-year-old female who died three weeks after delivery with generalized thrombotic phenomena following acute and subacute endometritis with retention of placental tissue. The uterine veins were involved by thrombosis which had extended into both common iliac veins, the inferior vena cava and inferior mesenteric vein. There were mural thrombi in both auricles and multiple emboli in branches of the pulmonary artery.

The symptoms are those of acute intestinal obstruction, strangulation, rupture of a viscus or peritonitis. In most cases the pain is agonizing, constant, and usually overshadowed the vomiting. In ordinary obstruction, vomiting is usually the prime symptom. Shock is most pronounced in patients with arterial occlusion. In general, the symptoms in cases of venous occlusion are of longer duration.

**Treatment**—There is no doubt that *resection* is the only hope for patients with involvement of an appreciable length of intestine by infarction. There are two types of cases in which operation is of no value: (1) Cases in which all of the



small intestine is deprived of blood supply, as in superior mesenteric occlusion, and (2) cases in which the patient's general condition is so desperate (due to co-existing heart disease, toxemia, or liver impairment) that any operative procedure is out of the question. Many more patients with resectable lesions could be saved by *correcting the reduced blood volume and treating shock* before attempting surgery. Transfusions of 2000 to 3000 cc. are indicated preoperatively. *Plasma transfusions* are also in order. To combat the post-operative propagation of thrombi, Murray has advocated the administration of *heparin* during and after operation. If resection is not done, it is dangerous to administer an anticoagulant because of the added blood and fluid loss into the lumen and peritoneal cavity. Exteriorization should only be carried out if the patient's condition becomes very critical during operation, or if there is an associated peritonitis.

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## SPLEEN

### Delayed Splenic Rupture

Some acute abdominal injuries have a latent period varying from a matter of hours to days or even weeks. During this latent period the patient may complain of an associated injury, such as a fracture of a long bone or a rib; he may be troubled by vague abdominal pain, or he may actually be almost symptom free. Then in typical cases a gradually developing splenic hematoma suddenly ruptures and the patient presents signs of collapse, shock, and severe anemia; if operation is not promptly performed, he dies. Delayed splenic rupture accounts for a higher percentage of all splenic lacerations. Splenic hemorrhage, immediate or delayed, is rapidly fatal unless immediate operation is performed, and is

therefore one of the gravest abdominal emergencies requiring surgical intervention. The latent period denotes the interval from the cessation of bleeding following the initial injury to the onset of secondary hemorrhage. Secondary hemorrhage occurs most often before the end of the first week.

**Symptoms and Signs During Latent Period**—In the present series of 66 cases of traumatic subcutaneous rupture of the spleen with delayed hemorrhage reported by Zabinski and Harkins,<sup>17</sup> pain was the outstanding symptom. It varied from abdominal discomfort to pain localized in the left upper quadrant, colicky or persistent. It was localized in the left upper quadrant in only four instances. Two patients were unable to stand erect because this position initiated the pain. Rigidity and tenderness during the first few days after the accident were uncommon findings. In only one case was there definite enlargement of the abdomen. Systemic signs of bleeding, such as pallor, malaise, faintness, sweats, and weakness were noted but were uncommon. Definite evidence of a perisplenic hematoma during the latent period was not present in any case. Quénu (1926) felt that a diagnosis of ruptured spleen could be made during latency on a person who, after receiving trauma to the left hypochondrium, presented a good general state but had some sensitivity in that area, a slight but persistent rigidity, and a slight elevation in temperature. Some found immobilization of the left lobe of the lung without pleural or pulmonary signs. In the present series, intrasplenic bleeding occurred before rupture of the capsule in over 50 per cent of the cases.

**Secondary Hemorrhage**—The symptoms and signs of splenic hemorrhage are those of peritoneal and diaphragmatic irritation, shock, and hemorrhage. It is



a matter of no small surprise to have an onset of severe pain or shock following minor exertion or apparently coming on spontaneously. It is ushered in with pain in the abdomen, chest, or shoulder. The abdominal pain, varying in severity, may be general or localized to the left side of the abdomen, left hypochondrium, epigastrium, upper part of the abdomen, or periumbilical region. Tenderness was generalized or localized to the left upper quadrant of the abdomen. Rigidity, when present, was more often general than local. Nausea and vomiting occurred in 17 cases. Collapse or shock resulting from hemorrhage soon follows or may be an initial sign; 15 patients had a white cell count ranging from 12,000 to 43,000. Berger stated that 51.8 per cent of patients with a ruptured spleen die within one hour as the result of hemorrhage.

**Treatment**—In untreated splenic rupture the mortality ranges from 77 to 100 per cent. When splenic laceration is suspected the patient should be kept at *rest in bed* under close observation for at least two weeks to lessen the possibility of delayed hemorrhage. All patients with ruptured spleen for whom a diagnosis can be made during the latent

period should have the benefit of immediate surgical treatment, and *splenectomy* should be performed. Adequate *treatment of shock with plasma or whole blood* forms a necessary adjunct to the operative procedure.

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## NEUROSURGERY

BERNARD J. ALPERS, M.D., AND H. EDWARD YASKIN, M.D.

### BRAIN ABSCESS

**Treatment**—Northfield<sup>1</sup> reviewed his treatment of abscess of the brain in 31 patients and found that of 12 patients treated by *drainage* only 3 lived, whereas of 19 patients treated by *aspiration*, *decompression*, or *enucleation* alone or combined, 11 survived. Thus, closed methods of treatment offer a much better prognosis than the open method. Fail-

ures are primarily due to such complications as multiple abscesses, massive edema, or acute meningitis. *Chemotherapy* combats meningitis but not the abscess proper. Successful treatment depends on accurate localization and a diagnostic burr hole, tapping or ventriculography. He believes that *aspiration* should be attempted first. The optimum time for surgical intervention

varies but operation should be resorted to whenever the clinical condition begins to deteriorate. Aspiration is followed by **decompression** only if tension is not relieved, if there is swelling of the brain, or if the abscess is deepseated. At the time of aspiration, the cavity of the abscess is irrigated with a 50 per cent electrolytic solution of sodium hydrochlorite. Repeated aspirations may be necessary, but the intervals between aspirations will gradually lengthen. Injection of 1 to 2 cc. (16 to 32 minims) of **thorium droxide** into the abscess may be of help in roentgenologic visualization of the organization of the wall of the abscess. Enucleation of an abscess depends on the formation of a well defined and tough wall. The optimum period varies, but the usual time is about the third month. Enucleation may prevent the occurrence of a convulsive disorder, and **anticonvulsants** should always be administered until the abscess is fully eradicated.

Grant<sup>2</sup> reported on the end results in 100 cases of brain abscess. He concluded that conservative treatment, **tap** or **tap and drainage** through a small trephine in the bone, produces the best results in the long run. The use of **wide open drainage** has not, in his series, lowered the operative mortality in comparison with more conservative measures. He feels that the initial attack upon a brain abscess should be carried out through a small trephine opening with the insertion of a drainage tube. If this technic does not produce satisfactory results, a resort must be had to more radical methods.

## BRAIN TUMORS

**Osteochondromas**—Intracranial tumors of cartilaginous structure are rare. Such lesions may arise from the men-

inges or from the bones of the skull. List<sup>3</sup> describes case histories of two groups of such cases: (1) primarily intracranial osteochondromas, arising from the sphenoid bone, and (2) primarily extracranial osteochondromas of the ethmoid or sphenoidal region with secondary intracranial extension. From the author's observations and the cases reported in the literature, it is evident that the base of the skull is a preferential location for osteochondromas. As a rule, these neoplasms become clinically manifest in young adults, between the ages of 20 and 30 years. Their rate of growth is slow, hence a clinical course over 10 or even 20 years is not unusual. If the tumor becomes malignant (osteochondrosarcoma) the course is apt to be rapid. The intracranial osteochondroma of the sphenoid produces a characteristic clinical syndrome. As a result of the parasellar location of the lesion, the structures in the wall of the cavernous sinus are affected. Pareses of the third, fourth, fifth, and sixth cranial nerves are nearly always demonstrable. Neuralgic pains in the distribution of the ophthalmic division of the fifth nerve and diminution of the corneal reflex are early signs. Sooner or later, the optic pathways become implicated. Depending upon the direction of the neoplastic growth, optic nerve, chiasm, or optic tract may suffer from pressure. Primarily extracranial osteochondromas show signs of an expanding lesion in the paranasal sinuses and cause neurologic manifestations only at an advanced stage.

The roentgenologic signs of this tumor are characteristic. The presence of basal osteochondromas is revealed by localized erosion of bone combined with dense calcifications in the tumor. Intracranial sphenoidal osteochondromas produce more or less marked parasellar

erosion, unilateral destruction or thinning of clinoid processes, and sometimes also erosion of the mesial portion of the lesser sphenoidal wing and the petrous apex. Since these tumors do not respond to *irradiation*, *surgical treatment* is the only promising form of therapy. Tumors of the intracranial parasellar variety are best exposed by *frontotemporal osteoplastic craniotomy* combined with *subtemporal decompression* after partial resection of the temporal lobe. Extracranial osteochondromas extending into the paranasal sinuses may, if small, be operated upon by the rhinologic method. Large lesions with intracranial extensions attacked by a combined intracranial and nasal approach may result in complications such as cerebrospinal rhinorrhea and meningitis. The postoperative period of survival may be a long one, unless the neoplasm has sarcomatous propensities.

**Pituitary Adenomas**—Alpers<sup>4</sup> emphasized that the crucial problem in both the diagnosis and treatment of pituitary adenomas was concerned largely with (1) the preservation of remaining vision, (2) the prevention of failure of vision in cases with adequate or normal sight. Two types of treatment are available—*operation* and *irradiation*. He believes that roentgen therapy is best reserved for the following types of cases:

1. Early cases:
  - (a) Cases with no optic atrophy, but with hemianopsia, with little or no loss of visual acuity.
  - (b) Cases with early optic atrophy with hemianopsia, but with normal, or nearly normal visual acuity.
2. Postoperative treatment.
3. Cases in which operation is refused.

When irradiation is used, it should be followed carefully for its effect on the optic nerve, visual fields, and visual acuity. Any indication of advance in any of these factors should mean substitution of operation for roentgen therapy. Most cases of pituitary adenoma require operation since the indications of pressure and visual loss are well advanced in most cases. Studies of postoperative cases show that for the chromophobe adenomas there is a great variability in the rate of growth. If a recurrence is to develop, signs of it will be manifest within five years after operation in 95 per cent of cases. With operation followed by irradiation there may be remission of symptoms for 10 to 20 years. In acidophilic adenomas associated with acromegaly, operation brings good relief of the visual disturbances, but none for the endocrine disorders. Cystic adenomas of the pituitary are not susceptible to irradiation. Operation gives best relief, but there is no way of determining beforehand whether a tumor is solid or cystic.

**Epidermoids**—Eleven of the 23 epidermoids and dermoids (cholesteatomas) of the central nervous system reported by Rand and Reeves<sup>5</sup> are instances of diploic or cranial epidermoids. As far as the authors know fewer than 200 epidermoids of the central nervous system have been reported. The intracranial variety is seldom diagnosed preoperatively. The extradural or diploic type can be recognized by roentgenologic studies. The diploic type is largely accessible surgically and the operative results are good. Although complete extirpation of these tumors is necessary to prevent recurrence, this often is not feasible with intracranial dermoids because of their extent and attachment to vital structures. The authors assert that the use of the term "cholesteatoma" is

unfortunate because it refers to a chemical by-product which is neither an essential nor an invariable constituent of these tumors.

**Paraphyseal Cysts** — Weinberger and Boshes<sup>6</sup> point out that the small, benign, encapsulated cystic tumors occupying the third ventricle of the brain formerly eluded diagnosis. **Cerebral pneumography** and modern refinements of neurosurgical technic have made possible the diagnosis and removal of these tumors. The authors reported the successful removal of a paraphyseal cyst, which brings the total number of reported surgical recoveries to 17. Paraphyseal cysts arise from the paraphyseal body, an ancient gland situated in the midline of the rostral portion of the roof of the third ventricle. A syndrome diagnostic of these tumors is lacking, but the occurrence of violent headache influenced by posture is regarded as significant. Operation for a paraphyseal cyst should be performed in one stage. Ample working room is obtained within the dilated lateral ventricle. The structures are seen clearly with the aid of illuminated retractors, which may be easily introduced within the ventricle. The foramen of Munro may be found by following the choroid plexus forward until it is seen to disappear. The cyst, if large, presents itself as a greenish or bluish mass in a dilated foramen. If small, it may not be visible and the foramen may appear as a small slit. By tugging gently on the choroid plexus, one can bring the cyst wall into view in the aperture of the foramen. Some operators first evacuate the thick colloidal contents of the cyst by aspiration, then deliver the capsule through the foramen. Others enlarge the foramen by slitting its margin. The slit can be made safely only in the anterior rim of the foramen.

The occurrence of cerebral swelling, as a consequence of operative manipulations, may require drainage of the ventricle for a few days with a Penrose drain or an indwelling catheter.

**Gliomas**—The treatment of patients suffering from gliomas of the brain is for the most part unsatisfactory. Rowe and Jacox<sup>7</sup> have been impressed by the good palliative results often obtained in seemingly hopeless conditions by **operation** and subsequent **irradiation**. They reported their experiences with 33 cases of verified gliomas. In a few cases of glioblastoma multiforme, when most of the tumor could be removed and extensive irradiation tolerated, worthwhile prolongation of the patient's comfortable and useful life occurred. Despite the radiosensitivity of medulloblastomas the clinical response to irradiation was less than anticipated. The failures seemed to result either from a tendency of the tumor to become radioresistant or the development of cord metastases which occurred in spite of intensive therapy. Approximately half of the patients in this series died within one year, regardless of surgical or roentgen treatment. However, at the present time it is impossible to determine before treatment is begun which patients fall into the hopeless group and which may be definitely benefited by treatment. The authors conclude that one is rarely justified in refusing operation or roentgen therapy or both even to the patient who presumably has an advanced, highly malignant, or deeply situated brain tumor.

Hawes and Mead<sup>8</sup> reported three cases of proved subtentorial brain tumors in which the lateral skull roentgenograms showed a posterior shift of the calcified pineal gland. They pointed out that one should bear in mind the possibility of this apparently paradoxical movement of the pineal which may be

due to internal hydrocephalus caused by obstruction to the outflow of spinal fluid through the aqueduct.

## CRANIAL TRAUMA

The recognition and treatment of shock, the use of sulfonamides, improved transportation of the wounded, and a more comprehensive conception of the physiological effect of trauma have almost revolutionized the treatment of wounds of the central nervous system. Transfusions of blood plasma and albumen administered in sufficient quantities to combat shock have made possible the transportation of patients over long distances. The emergency treatment of open head wounds consisting of *shaving the scalp, arrest of hemorrhage*, and local application and oral administration of *sulfonamides* have allowed for an interval of from 36 to 48 hours before reparation surgery is imperative. Craig<sup>9</sup> believes these two factors have not only lowered the mortality and reduced the incidence of infection, but have changed the plan for the care of these cases.

### Acute Craniocerebral Trauma

**Gunshot Wounds of the Head—**Money and Nelson<sup>10</sup> reviewed their observations of 78 cases of all types of head wounds which were treated in 1942 during the fighting in the vicinity of El Alamein. They emphasized the fact that the thoroughness of the initial examination and toilet of the wound has proven to be more important than the time factor, at least up to four days, as long as prophylactic *sulfonamide therapy* is maintained during the period of waiting. The removal of indriven bone fragments and inorganic debris is more important than the extraction of metallic foreign bodies. They found that even minute missiles, making a small wound

in the scalp and outer table of the skull, were apt to drive large comminuted pieces of the inner table deeply into the brain and to cause more extensive damage than the size of the missile and the condition of the patient would indicate. They recommended closure of the tear in the dura mater in order to prevent the formation of hernia cerebri, cerebrospinal fluid fistula, and aerocele. They stressed the importance of maintaining an adequate concentration of sulfonamides in the cerebrospinal fluid.

Ascroft<sup>11</sup> reported on the results in 516 cases of gunshot wounds of the head treated in the Middle East. Despite the difficulties arising from the terrain and long distances for evacuation, it was possible to operate on nearly one-half of the cases at the Base within 72 hours. The mortality in the series was 9.1 per cent. The figures given brought out the importance of *thorough operation*. The results of cases operated upon primarily by a neurosurgical unit equipped with suction diathermy and other special equipment were better than the results of cases operated on earlier in the forward areas. If there is reasonable prospect of evacuating the cases within 72 hours of injury, it is better to do nothing in the forward area except to *dress the wound* and give *sulfonamides*. If transportation must be delayed beyond 72 hours a modified operation was deemed advisable: the *"open toilet" procedure* entailing excision of devitalized scalp, removal of dirt, débris, and loose fragments of bone and metal, which are visible, easily accessible, and removable without provoking hemorrhage. The wound should be left open. Upon arrival of the patients at the Base hospital it was necessary first to assess the state of shock to permit immediate institution of the necessary treatment, and then to determine the

state of consciousness, which the author described as the most useful index for establishing priority of treatment among serious cases. The next step was x-ray examination. As a rule at operation, devitalized scalp was excised more widely than is done in civilian accident cases because in these deep missile wounds, layers are more extensively destroyed than the superficial ones. The loose fragments of depressed and penetrating fractures were removed piecemeal. If the dura had not been penetrated, it was not opened unless there was evidence of cerebral compression. If the dura was open, it was rarely necessary to enlarge the opening, but loose tags of dura were excised and bone fragments were gently sucked out, thus removing damaged brain clots, and some of the foreign bodies. No attempt was made to remove deep-seated metallic fragments but loose fragments of bone driven into the brain were removed because of the danger of abscess. The dura was never closed. Clean wounds of the scalp were closed with a layer of stitches in the galea and one layer in the skin. A corrugated rubber drain was led out through a stab wound. Frankly septic wounds were left open. In the field the sedative of choice was *morphine*, 0.016 Gm. ( $\frac{1}{4}$  gr.), intravenously. *Paraldehyde* was effective during transport or the post-operative period. At operation intravenous *pentothal* was adopted. The patients were encouraged to get up and get busy as soon as they felt so inclined. This helped to minimize the significance of brain injuries in the minds of the patients.

Glidden<sup>12</sup> reviewed the aftereffects of gunshot wounds of the head in 500 Canadian pensioners from the first World War. A study of these cases showed the incidence of epilepsy of 9.8 per cent. Where the dura mater had been

torn the incidence of epilepsy was increased to 18.9 per cent. Retained foreign bodies apparently increased the incidence of epilepsy — retained metal being the cause of epilepsy in 26.1 per cent and retained bone in 66.7 per cent. The type or location of the injury did not seem to affect the subjective complaints, as 87.6 per cent showed a record of headache. Operative procedures after discharge from the army did not seem materially to affect these complaints. Of these patients 58.4 per cent had complaints of dizziness.

**Postmortem Examination** — Gurdjian and his associates<sup>13</sup> reported the results of observations made on post-mortem examinations of 151 patients who died following cranial trauma. They found that in almost every instance of fatal head injury there was a combination of pathological processes; thus, epidural hemorrhage, petechial hemorrhages, and cerebral bruises were found frequently to co-exist. There was great variation in the extent and severity of brain lesions in the fatal cases. A massive intracranial hemorrhage due to trauma was usually on the surface of the brain and could have been amenable to surgical treatment. Large intracerebral clots were rare. In epidural hemorrhage, exploration about a fracture line seemed advisable. In subdural hemorrhage the fracture line was of little value in localization, often being opposite to the side of the subdural hemorrhage.

**Compound Fractures** — Munro<sup>14</sup> presented an analysis of treatment of 218 cases of all types of compound fractures of the skull. Complete *débridement* is recommended within 48 hours of the time of infliction of the injury or else no operation until the wound is completely healed for 6 to 8 months. The patient should not be operated upon until he is out of surgical shock and

until the general condition warrants it. After the diagnosis has been made by palpation through the wound, the first and only dressing prior to débridement must be one that can be applied with the absolute minimum of handling. The débridement must be done in such a way as to avoid the spread of bacterial contamination throughout the wound and the production of tissue necrosis; it should include the removal of all large foreign bodies. No wound that has been properly débrided should be drained. Irrigation of the wound before and during operation is condemned. Chemotherapy in the form of *sulfanilamide* or *sulfadiazine* is recommended both by mouth and in the wound, but only as an adjunct to properly conceived and executed surgery. *Sulfathiazole* should not be used in craniocerebral wounds because of its irritating effect on the cerebral cortex.

Pickles<sup>15</sup> reported his conclusions based on the observation of 104 cases of compound fracture of the skull. He feels that infection in this type of case can be largely avoided by the following methods: (1) minimal handling of the wound; gentle exploration of the external wound with a sterile gloved finger to determine the presence of fracture and then covering it with a dry sterile gauze without attempting to clean out before operation and without blocking the drainage of ear, nose, or pharynx; (2) avoidance of reversal of drainage and no lumbar puncture or dehydration until 10 days after arrest of bleeding or drainage of cerebral spinal fluid, the same precautions being observed for 10 days when there is no external bleeding or drainage; (3) early operation within six hours of injury when necessary, shock having been brought under control; (4) thorough débridement and mechanical cleansing; (5) avoidance of

surgical drainage (except in wounds of the frontal sinus).

**Gas Infection**—A Committee of Soviet scientists<sup>16</sup> reported their results in the treatment of gas infection of the brain which was one form of serious complication of craniocerebral injuries. Of their 39 cases of anaerobic cerebral infections, 17 died. The clinical picture of infection of the brain by gas-forming anaerobes was characterized by the following signs and symptoms: (1) gas gangrene; (2) discharge of necrotic brain tissue and debris from the wound; (3) colorless watery purulent discharge; (4) acute and putrid smelling of the wound; (5) formation of gas in the wound; (6) edema; (7) prolapse; (8) meningitis; (9) low temperature with rapid pulse; (10) abscesses; (11) severe "bursting" headaches (12) blood picture (increase in the number of lymphocytes); (13) nausea and vomiting; (14) delay in the formation of granulation tissue. They recommended the use of the following treatment: (1) prophylactic *antigas gangrene serum* in doses of 5000 to 10,000 units; (2) timely use of *sulfonamides* locally and as an emulsion in castor oil or cod liver oil, 10 Gm. (150 gr.) *sulfanilamide*, 10 Gm. (150 gr.) *sulfathiazole* in 80 to 100 cc. (3 to 3½ fl. oz.) of castor oil; *sulfathiazole* orally 6 Gm. (90 gr.) daily for six days; intravenously, 1 per cent solution of *sulfathiazole* 30 to 40 cc. (8 to 10 fl. dr.) two or three times in 24 hours. They concluded that the best results in gas infection of the brain were obtained by active surgical intervention and the use of *antigas gangrene serum*. They dealt boldly with the excision of prolapsed brain tissue, the gas infection, and the removal of necrotic tissue, applying *sulfanilamide* and *sulfathiazole* emulsion to the cavity. If meningeal involvement occurred they gave sulfon-



amides intravenously and intrathecally. Signs of agranulocytosis in the blood were treated with *transfusion* but without stopping the active sulfonamide therapy. Very often with this complication the sulfonamide dose was reduced and in order to lessen the toxic effects on the blood, transfusions of 250 to 350 cc. of blood were given, using anti-gas gangrene serum at the same time.

**Traumatic Cerebral Fungus** — O'Connell<sup>17</sup> reported on the treatment of traumatic cerebral fungus. Before considering the treatment of the fully developed cerebral fungus it should be emphasized that this complication of a head injury is, in most instances, avoidable. Early *surgical treatment* of a penetrating wound will prevent its development. Such treatment should consist of excision of the scalp edge, excision of the margins of the bone defect en bloc, and removal of devitalized brain, blood clot, and foreign bodies from the cerebral wound. Accurate suture of the scalp wound in two layers should then be carried out whenever possible. If destruction of scalp be too extensive to prevent this, it may be possible to cover the exposed cerebrum with a scalp flap, while a Thiersch graft is placed over the denuded area of cranium. *Lumbar puncture* is advisable at intervals after such operations in order to relieve the suture line from tension and thus prevent the development of a fungus which would be inevitable if primary healing of the scalp wound did not occur. If cerebral fungation occurs, there are three essential features of treatment that O'Connell recommends. These consist of: (1) *combating the infection* of brain and meninges; (2) the *minimizing of injury* to the exposed tissue; (3) the control of the tendency for progressive fungation to occur by *repeated lumbar punctures*. The author ad-

vances the hypothesis that ventricular dilatation is a causative factor. This ventricular dilatation is itself produced by the alterations in intraventricular pressure which occur with each cardiac and respiratory cycle.

### Closed Head Injuries

**Cerebral Contusion**—Rogers<sup>18</sup> presents evidence which indicates that the brain reacts to cerebral contusion by attempting to increase its volume. *Dehydration* is a method of choice in this type of case. It should be effected by rectal administration of *magnesium sulfate* and not by intravenous methods which he believes probably cause undesirable reactions.

**Cerebral Concussion** — Guttmann and Horder<sup>19</sup> reported on the after-effects in 60 cases of head injuries in children. Fractures of the skull were more frequent than among adults. In the active stage emotional symptoms were more impressive than clouded consciousness and intellectual loss. The incidence of headache did not differ much from that in adults. Two-thirds of the cases were fit for discharge after two weeks of treatment in the hospital. The postconcussional syndrome was observed in 10 per cent of the cases, its incidence depending to a large extent on environment factors. The accidents of all children in this group were comparatively mild and all of the cases showed psychologic or social features which seemed adequate to account for the continuation of the symptom. Irritability was the most common aftereffect. Persistent behavior disorder was rare in this series of cases as also was intellectual impairment.

Shearburn and Mulford<sup>20</sup> reported the results of treatment of 90 acute head injuries with cerebral concussion observed in Casablanca, North Africa.

Unconsciousness varied in degree from momentary loss to complete loss for 96 hours in these cases. For purposes of analyzing the *early ambulatory method of treatment*, the patients were divided into two groups: group A included patients on whom it was possible to use the method and comprised 72 patients with head injury only or with head injury and some other injury not requiring bed rest. Group B included cases in which it was not possible to use the early ambulatory method. They pointed out that the incidence of post-traumatic intracranial hemorrhage is not increased by allowing the patient to be ambulatory soon after the return of consciousness. This observation, they felt, was verified by their cases. They also felt that the incidence of postconcussion symptoms seemed to have been greatly reduced by early ambulatory treatment.

### Subdural Hematoma

Abbott and his colleagues<sup>21, 22</sup> reported on hematoma following blast injuries. The authors observed a number of patients suffering from the concussion effect of a nearby shell, bomb, or underwater explosion, who developed an accumulation of fluid in the subdural space. The patients gave a history of exposure to severe concussion, loss of consciousness, persistent headache, memory loss, and irritability. The most common neurologic finding was a slight facial palsy, a transient hemiparesis, and occasionally a transient change in reflexes. The most pronounced symptoms were persistent, usually generalized, headache, a history of coma, syncope, or convulsions, and a definite departure from a stable personality. In some of the cases bilateral effusion of small amounts of old blood and several ounces of xanthochromic fluid were found. The authors called these findings a subdural effusion

rather than a true subdural hematoma. Ten cases were operated upon following exposure to a severe blast concussion. Of these ten cases, seven had subdural effusions and in two instances subdural hematoma occurred. In one case both conditions existed.

Hamlin<sup>23</sup> suggests that a blast wave of sufficient magnitude may be transmitted to the spinal canal and thence to the cranial cavity to set up a convection force in the cephalad direction through the spinal fluid and possibly the neuroaxis itself which may be analogous to the phenomenon of cerebral acceleration that follows a blow to the head. Such a mechanism could damage the supporting vessels of the leptomeninges, giving rise to subarachnoid hemorrhage and neurologic symptoms. In three cases spinal tap revealed red blood cells and slight elevation in total protein four to six days after injury.

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## CRANIOPLASTY

The cranial defect in military surgery represents a very important problem because of the frequency of its occurrence. Recent writers<sup>24, 25</sup> have reported on the use of *tantalum*. Tantalum is element 73 on the periodic table. It has primarily the physical properties of cold rolled steel and the chemical properties of glass. It can be secured in plates or sheets in any size desired; the thickness should be 25 mils. It is inert and can be cut, bent, or hammered and it can be sterilized by boiling or by any recognized chemical method. It will give protection at the thickness of 25 mils which will approximate that of the normal cranium. Pudenz<sup>24</sup> implanted tantalum plates into the cranial defects of 11 cats. His experimental studies indicated that tantalum is a satisfactory alloplastic material for the repair of

cranial defects. It has the desirable qualities of noncorrosiveness, inertness in tissue, nonabsorbability, absence of toxic ingredients, and malleability. Fulcher<sup>25</sup> reported on the use of this substance as a metallic implant to repair cranial defects as applied to patients.

## SPINAL CORD INJURIES

**Thoracic and Lumbosacral Cord Injuries**—Munro<sup>26</sup> reported on his observations of 40 cases of thoracic and lumbosacral cord injuries. Twenty-three of these patients died in the hospital. He feels that certain general principles of treatment must be adhered to if the end results, which the patient has the right to expect, are to be obtained. (1) Every patient with spinal cord injury should have his bladder emptied and an inlying catheter fastened in place at the earliest possible moment. As soon as possible thereafter this catheter should be attached to a *tidal drainage* apparatus properly adjusted by a systometry to the needs of the individual bladder. (2) Simultaneously with this the patient should be *treated for surgical shock* if and when it is present. (3) Splints, no matter what their material, that are fixed in relation to the patient, must never be used in spinal cord injury. The application of plaster of Paris is contraindicated regardless of the amount of padding used. Metal frames for hyperextension or any methods which aim to accomplish rapid hyperextension are also contraindicated. (4) Sufficient *protein* must be given these patients in their diet or by transfusions to maintain their serum protein at 6.0 mg. or better. (5) While the patient remains on tidal drainage his *fluid intake* should never be allowed to fall below 4000 cc. in 24 hours. Their *salt intake* must usually

be increased also, and they should be given large amounts of *vitamins*. Care must be taken to *keep the bowels open* and to prevent the development of fecal impaction. (6) All patients must be moved off their backs and on to one or the other side every two hours day and night during their stay in bed. They should never be allowed to lie in a wet bed for even as a little time as 15 minutes. (7) Other procedures will depend upon the presence or absence of a positive *Queckenstedt test*. This must be determined in every case without exception and should be carried out after the patient is out of surgical shock and on tidal drainage. If there is no block there is no need for operation. The x-ray examination can and should be postponed for from four to six weeks. (8) The patient should be placed on a sponge rubber mattress on top of a hair mattress and bed board with the bed made up in the usual manner, his feet supported at right angles and with the bed clothes held off them by a cradle, his knees held on pillows in slight flexion. (9) *Physical therapy* can be started if the patient's muscles are not hypertonic.

**Cord-Compressing Injuries**—Fleiss and Ingham<sup>27</sup> reported the occurrence of cord-compressing lesions with a normal Queckenstedt sign. Thirty per cent of the series of 20 patients having a cord compressing lesion gave no evidence of spinal block.

**Paralysis of the Bladder**—Riches<sup>28</sup> recommended suprapubic catheterization for paralysis of the bladder in spinal injury. He described the simple instrumentarium and the technic. After paralysis from spinal cord injury the bladder should be allowed to distend. When it is distended, *suprapubic catheterization* should be performed. *Tidal drainage* should be added after two

days. The use of a urethral catheter in the treatment of the paralyzed bladder, he feels, should be forbidden.

### HERNIATED INTERVERTEBRAL DISK

**Diagnosis**—For Dandy<sup>29</sup> the diagnosis of a ruptured disk was almost pathognomonic from signs and symptoms alone. He further believes that iodized oil and air injections into the spinal canal are not indicated. Only the suspicion of a tumor justifies a lumbar puncture. Ninety-eight per cent of all protruding lumbar disks are at the fourth and fifth interspaces. He stated that if there is a diminution or absence of an Achilles reflex, the disk involved will be at the fifth in most instances. About 20 per cent of all patients with ruptured disks have two herniations, one at the fourth and the other at the fifth. The unusual disks at the second and third are usually localized by pain in the front of the thigh; the others give pain in the back of the leg. The cure of a ruptured disk requires removal not only of the protrusion but of the entire necrotic interior by thorough curettment. He feels there is no indication for fusion operations. He discards the diagnosis of hypertrophied ligamentum flavum as a cause of the sciatic syndrome.

Yaskin and Tornay,<sup>30</sup> on the other hand, express surprise at the fact that some clinicians regard the diagnosis of a protruded disk as a simple matter. They point out that there are many and varied conditions which may reproduce the symptom complex of a protruded disk or disks. To these authors it seems that the utter disregard of contrast medium studies prior to operation for the majority of cases is at present untenable. Based on their experience with 50 operated cases for this condition, they

suggest the following criteria for diagnosis and indications for operations: (1) exclusion of other definite causes; (2) a suggestive history; (3) the presence of at least some objective abnormalities; (4) previous adequate orthopedic or other treatment for a reasonable time (three to six months) with no improvement in disability; (5) the presence of a major disability; (6) lasting recurrent attacks of moderate disability or frequent attacks of major disability; (7) contrast medium studies prior to operation for the majority of cases. Weber<sup>31</sup> in his review of the present status of contrast myelography concluded: (1) a completely satisfactory medium for contrast myelography has not yet been discovered; (2) for accurate examination of the entire spinal canal, lipiodol remains the most satisfactory; (3) air myelography has limited but definite value, mostly for the examination of the lumbar region to detect protruded intervertebral disks; (4) contrast myelography has value only when the findings are compatible with the clinical and neurologic findings. He took exception to Dandy's statement that there be abolition of all contrast myelography in the diagnosis of protruded disk.

Hyndmann and his co-workers<sup>32</sup> emphasized the fact that low back pain accompanied by sciatic radiation may be due to (a) lumbosacral root compression. A herniated disk is the commonest causal factor. The pain is referred and is ordinarily accompanied by other symptoms and signs of nerve root compression. If a tender locus is present over the lower part of the back, sacrum, or buttocks, local anesthetization with procaine of the locus will not abolish the symptoms or signs. (b) Myofascial trauma. The radiating pain in this case is reflected. The procaine test will abolish the pain temporarily and thus indi-

cate the causal factor. Hence, the procaine test is valuable in the differentiation of referred and reflex "sciatica." The authors stated that herniated disk below the fourth or fifth lumbar vertebrae ordinarily invokes such a definite syndrome that myelography is seldom indicated. In the equivocal case they utilize 5 cc. of iodized poppy seed oil for contrast myelography.

**Symptoms**—Haynes<sup>33</sup> outlined a schedule of preoperative, operative, and postoperative technics which has proven successful in a series of soldiers with herniated intervertebral disk. The most reliable symptom of the condition presented was pain in the back or in the legs following the distribution of the sciatic nerve or, more usual, pain in both regions, usually following a minimal amount of trauma. This symptom complex was made worse by coughing or sneezing. The important objective signs consisted of tenderness of the spinous processes overlying the disk suspected, a positive Laségue's sign, and a diminished or absent Achilles reflex. Anesthesia or hypesthesia of the calf or foot on the involved side was of considerable value, if present, but its absence was not significant. The value of spinal fluid protein was significant if it was increased, but a normal value did not in itself constitute evidence against the presence of a protruded disk. The flat roentgenograms of the spinal column were of no value. Pneumomyelography was more likely to mislead than help. No contrast medium myelography was used.

**Prognosis**—He found that one must have a patient who is psychiatrically sound before considering operation. He states that a patient with any symptoms of emotional or mental unsoundness, regardless of the facility of the surgeon or the subsequent relief of pain, will not

make a recovery after operation. He emphasized psychiatric evaluation in each case. He stressed the fact that as little bone as possible be removed during the operation since the back must not be weakened.

**Treatment**—A *partial laminectomy*, preserving the spinous process, proved best in his experience. He operated at the level indicated by the distribution either of the pain or of sensory change. If a laminectomy has been extensive, a situation which should be the exception, a fusion may be considered, although it has not increased the percentage of cures. Facet fusion has not increased the percentage of cures. The postoperative care of these patients is as important as the preoperative evaluation of their condition. They should be kept in bed for 14 days and be provided with a tight, well-fitting *lumbosacral belt* before being allowed up. They should be allowed about the ward for one week following the period in bed and then given a 30-day furlough, during which time they are advised to wear their belts and to resume gradually their former degree of activity. Following this period, they should be given about two weeks of extensive *physical therapy*, including exercises designed to strengthen the back and muscles, and to increase the degree of boxy flexion.

Love<sup>34</sup> studied 1,500 cases of protrusion of an intervertebral disk. He found the results of operative therapy excellent. The diagnosis was confirmed by contrast radiologic studies, with use either of air or of an opaque oil.

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## NERVE INJURIES

Wounds of the peripheral nerves are, and will be, one of the major problems of the war. Injuries of the extremities comprise the majority of disabling

wounds, and associated with them is a high percentage of peripheral nerve injuries. While at the present time an end-to-end anastomosis is the operation of choice, using nonabsorbable sutures, fibrin glue and nerve grafts are being investigated. Peripheral nerve damage produced by war wounds differs from that due to peacetime injuries because of more extensive destruction and maceration of tissue, and late repair.

Craig<sup>35</sup> concluded that satisfactory regeneration of severed nerves depended upon prompt, accurate, bloodless, aseptic *end-to-end anastomosis*. When such an ideal situation does not exist, both ends of the nerves may be sutured as close together as possible, and the nearby joint flexed. After gradual extension of the joint over a period of weeks, a secondary operation to approximate the ends may be successful. Nonabsorbable sutures such as silk, cotton, steel, and tantalum wire, are more satisfactory because they produce less reaction and hold more firmly than catgut. The effect of *sulfonamides* has proven beneficial and they are used extensively in infected or potentially infected wounds. This does not inhibit nerve regeneration and allows for infection to clear. A thin film of *sulfanilamide powder* blown into the wound is absorbed, the nerve sutured, and the wound closed without drainage. Secondary sutures have been accomplished with success and usually performed when there is no evidence of regeneration to the nerve after a period of observation from two to six months. *Plastic repair* and *tubulization* was tried with discouraging results. *Autogenous nerve grafts* were used with some success in the repair of the facial nerve by utilizing multiple grafts made from a smaller nerve as well as a graft of the same caliber. Brachial plexus injuries following gunshot

wounds tended to recover spontaneously since they were usually due to concussion, hemorrhage, or stretching. Therefore, operative treatment should be delayed for a reasonable period.

Higbet and Holmes<sup>36</sup> pointed out that there is a limit to the size of the gap which can be closed by the method described by Craig. They concluded from their clinical and histologic study that although end-to-end suture may be possible by appropriate technic, no useful recovery can be expected if the length of nerve resected is so large as to necessitate great postoperative stretching. They advise that in cases where, at either early or late exploration, the resection necessary is extensive, 10 cm. or more, suture is not justifiable and alternative measures such as *nerve grafting* should be considered.

Weiss and Taylor<sup>37</sup> reported on their work with dehydrated nerve grafts. Experiments were performed on nerve repair in various animals. Practically ideal nerve regeneration has been obtained by sutureless splicing of nerve stumps by means of sleeves of fresh or frozen-dried artery. The success of *sleeve-splicing* is based on the collection within the sleeve of endoneural exudate which constitutes a superior growth medium for sheath cells and nerve fibers. In bridging nerve gaps by grafts, sleeve-splicing has given good results. Moreover, Weiss has developed a method by which nerve fragments can be stored indefinitely without losing their usefulness as grafts. The nerves are frozen at  $-150^{\circ}$  C., dehydrated in a high vacuum, sealed in and stored in the dry condition, then rehydrated before use. When grafted, such nerves are readily and fully pervaded by regenerating nerve fibers, much as if they were living. The development of this technic for storing nerve grafts and the

introduction of less difficult methods for fixing grafts, such as the plasma "glue" described by Seddon and Medarvar (SEE: 1943 *Service Volume*), may lead to a more extensive clinical trial of *grafting* for peripheral nerve injuries.

Klemme and his co-workers<sup>38</sup> reported on their experience with autopsy nerve grafts in peripheral nerve surgery. They made a clinical application of the "glue" suture technic. The glue used was 50 per cent acacia prepared by slowly dissolving the acacia in boiling distilled water. This percentage gave a thick glue when cooled to room temperature. This preparation could be autoclaved. The cadaver grafts were obtained under sterile conditions in the autopsy room. Two patients already have yielded good clinical results after the application of these *cadaver nerve grafts*, using the acacia preparation to glue the severed ends together. Tarlov and Benjamin<sup>39</sup> found that cockerel or human plasma clot suture of nerves in rabbits generally resulted in more inflammatory and fibrotic reaction than did silk suture. However, autologous plasma clot suture of nerves in rabbits and dogs usually resulted in very little inflammatory or fibrotic change. Nerve fibers readily grew through the junction formed by means of plasma clots. They concluded that plasma clot suture offered promise as a method of securing junction of nerve ends with minimal distortion of nerve pattern in instances in which the factor of tension at the suture site can be eliminated. Guttmann<sup>40</sup> found that woman's hair and plain white silk of finest size were least irritating materials for nerve sutures. His experiments confirm that *through-and-through sutures* should be avoided whenever possible; the method of choice was *epineural suture*.

## SURGICAL METHODS FOR RELIEF OF PAIN

Grant,<sup>41</sup> in an excellent review of this subject, stated that complete and permanent relief of otherwise intractable pain may be accomplished by severing the afferent pathways, but the dangers of such procedures must be carefully balanced against the anticipated benefits. When life expectancy of a patient with cancer is less than three months, or if the lungs are involved, operation is not indicated and subarachnoid injection of alcohol or use of opiates is preferable. Patients with pain in the face, jaw, mouth, and sinuses, with or without metastases to the cervical glands, usually have the afferent pathways of the trigeminal and glossopharyngeal nerves and upper four or five cervical posterior roots involved. Before the trigeminal nerve is cut, *alcohol injection* should be attempted, especially in trigeminal neuralgia, to establish the diagnosis and to accustom the patient to the sensation of anesthesia of the face. When the pain is referred to the tongue or floor of the mouth, block of the third division is indicated. If this procedure is unsatisfactory it may be followed by cutting the superficial cervical roots where they swing forward over the sternomastoid muscle. If trigeminal alcohol block is unsuccessful, section of the sensory root or preganglionic division of the second and third branches is done by subtemporal approach under local anesthesia. Ninth nerve involvement is indicated by pain in the base of the tongue, tonsil, or throat, and can be relieved by sectioning the nerve through unilateral suboccipital *craniectomy*; by extending the incision downward, the upper three cervical roots can also be exposed and cut if indicated, or better yet, intramedullary *tractotomy* on the descending root of the trigeminal can be done. Intense



pain due to invasion of the brachial plexus can be relieved by severing the posterior roots from the third cervical to the first thoracic segments. The alternatives for *rhizotomy* are the dangerous and extensive high cervical *cordotomy*, section of the pain fibers in the medulla or in the cerebral crus, or cordotomy and rhizotomy. For pain referred below the level of the ensiform cartilage, cordotomy of the anterolateral spinal columns, at or just above the level of the first thoracic segment which is above the point of entrance of sympathetic fibers to the cord, will usually give relief. The exact level for cordotomy can be determined by the height of spinal anesthesia necessary for relief of pain. If the operation is performed under local anesthesia, accurate level of analgesia can be tested as the tracts are incised. Bilateral section should be done at different levels to prevent transverse myelitis. The effects of subarachnoid alcohol injections are unsatisfactory in that pain is not certainly relieved and sphincter control may be destroyed. If unilateral cordotomy is subsequently necessary, complete bladder retention may ensue because of the damage to sphincter fibers by the previous alcohol injection.

Walker<sup>42</sup> reported on his operation of *mesencephalic tractotomy* for relief of intractable pain. He makes an incision in the rostral portion of the pons, interrupting the pain tracts at this level. This level is more favorable, he feels, because section is accomplished easier in view of the fact that the surface markings of the pain tracts in the mesencephalon are clearer. Immediately after section, superficial and deep pain in the contralateral half of the body were relieved. One or two days after operation hemianopsia contralateral to the lesion is usually present. This clears within a

week or two. Peyton<sup>43</sup> found that of 59 patients having *subarachnoid injections of alcohol*, 33 obtained complete relief, 15 partial relief, and 11 no relief. Complete relief was obtained by 81 per cent of the patients having *cordotomy* for the relief of pain from incurable cancer. Hyndman and Wolkin<sup>44</sup> reported that anterior cordotomy (section of the anterior and anterolateral columns) at the first dorsal segment combined with section of Lissauer's tract ordinarily brought the level of analgesia to the first dorsal dermatome and was useful in abolishing pain high in the chest. Weinberger and Grant<sup>45</sup> reported their results with *intramedullary tractotomy* for the relief of facial pain. They found it necessary to modify the operation originally suggested by Sjoqvist in order to avoid injury to the restiform body and cuneate tubercle with resultant disturbances in equilibrium and body posture. They recommended placing the incision about 12 mm. more caudally in the medulla. In a number of their cases they were able to abolish the symptoms of trigeminal neuralgia with the modified Sjoqvist technic.

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## ORTHOPEDIC SURGERY

JOHN ROYAL MOORE, M.D.

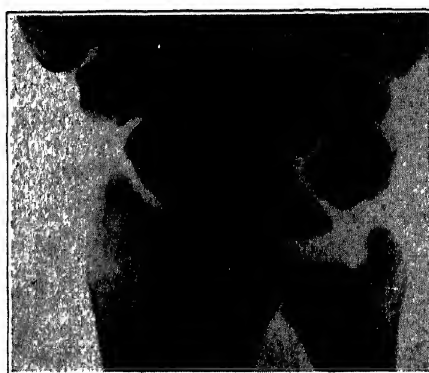
### BONES

**Aseptic Necrosis of the Lunate Bone**—Roth<sup>1</sup> reports a very complete and detailed study of the pathological changes noted in a case of Kienbock's

disease, aseptic necrosis of the lunate bone, first described by Kienbock in 1910. The histological picture was first described by Baum in 1913 and Axhausen added further confirmatory evidence to

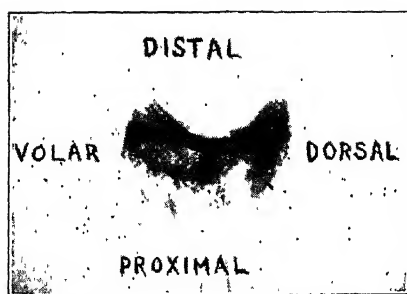


A

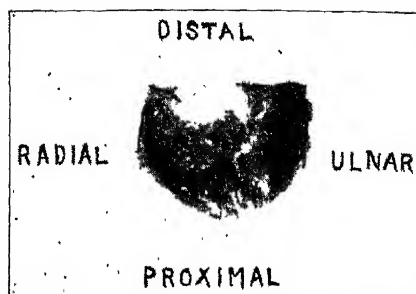


B

Fig. 1—A, The contour of the right lunate bone has been altered by the depression of the radial half of its proximal articular surface. A fracture line is present on the deep surface of the depressed fragment. Two small, irregularly rounded, rarefied areas appear toward the wrist joint articulation. The density of the bone is on the whole increased. (The lateral view shows a decrease in the short axis of the bone.) B, Six months later. (Rarefaction has increased centrally and density has increased peripherally. The contour of the bone shows progressive alteration from the normal. (F. B. Roth: *J. Bone and Joint Surg.*)



A



B

Fig. 2—*A*, Lateral roentgenogram demonstrates decreased density of the proximal portion and part of the central portion, and generally increased density of the distal part of the bone. A fracture is visible on the distal surface. *B*, Anteroposterior view taken with the x-ray tube tilted obliquely in the axis of the arm demonstrates a fracture line running from the proximal to the distal aspects and having a branch extending out to the radial side. (F. B. Roth: J. Bone and Joint Surg.)

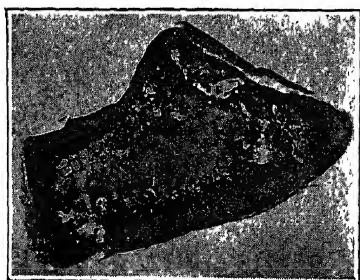
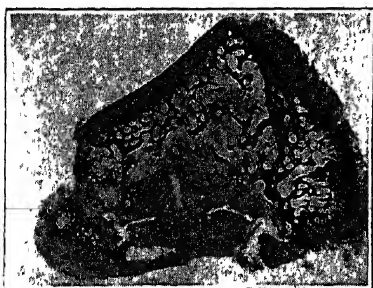


Fig. 3—Serial sections of the excised lunate bone ( $\times 2\frac{1}{2}$ ). Compare with Fig. 2 *B*. The proximal and central areas of the lunate are the most modified. (F. B. Roth: J. Bone and Joint Surg.)

the history of aseptic necrosis in 1924. In the author's case, the lunate bone was removed and the pathological examination of the excised bone showed extensive aseptic necrosis, collapse, and invasion by vascular fibrous tissue. The articular cartilages were modified and there was no evidence throughout the bone of ununited fractures. Secondary arthritic changes were occurring.

**Comment**—The value of this presentation lies primarily in the fact that it adds further knowledge to the pathology of this condition and possibly offers an explanation for the pain symptoms (fractures and arthritis combined).



Fig. 4—Microscopic section from ankle of male deceased twin at 10 months. (G. Raap: Am. J. Roentgenol.)

**Chondrodystrophia Calcificans Congenita**—Raap<sup>2</sup> reports two cases of chondrodystrophia calcificans congenita. Calcium, phosphorus, phosphatase, cholesterol determinations, blood count, and serology were negative. Microscopic reports stated that "sections showed increase of fibrous tissue of periosteal character. Directly under this periosteum, a formation of cartilage was noted. The deepest layers of cells from osteoid tissue which is partly calcified."

The history of this condition is briefly reviewed. Conradi in 1914 discussed

what was probably the first case. Tisdale and Erb in 1924 reported two cases, "the first of which at five weeks presented roentgenographically 'peculiar irregular calcareous deposits in the epiphyses at both ends of the humeri, the proximal ends of the radii, ulnae, tibiae, fibulae, and the distal ends of the femora.'"

Geyman, Hunerman, Reilly and Smyth, and Maitland have reported cases. The abnormal calcifications are noted at birth

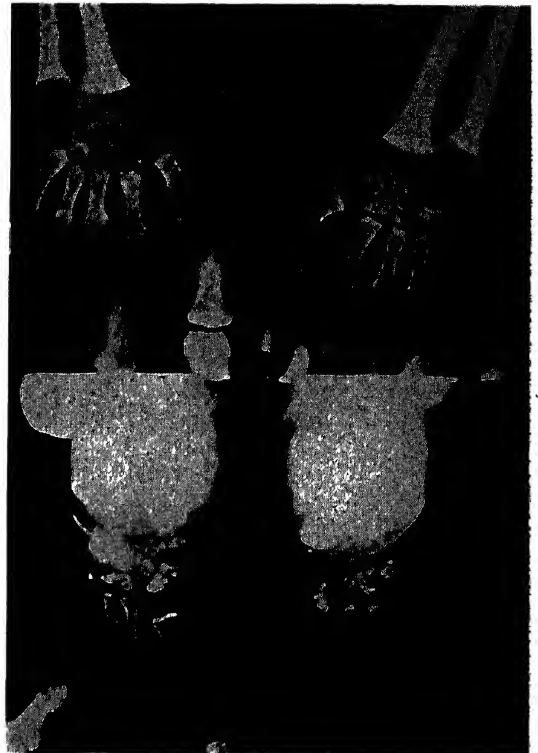


Fig. 5—Living twin at 10 months. Note calcific deposits in wrists and ankles. (G. Raap: Am. J. Roentgenol.)

and usually disappear about the age of three. There is moderate shortening or dwarfing of the long bones.

**Decompression Diseases of Bone**—Allan<sup>3</sup> points out that "during ascent in an airplane, the tissues become supersaturated with nitrogen because the partial pressure of nitrogen in the lungs falls off. As this pressure is released the nitrogen comes out of solution in the body and appears in the tissues and in

the blood in the form of bubbles. Since the elimination of nitrogen from the body is entirely through the blood stream, those parts of the body which have the poorest blood supply will be the slowest to lose their excess nitrogen. Bone is the tissue with the poorest blood supply in relation to the nitrogen content. There are two areas in bone where anastomotic



Fig. 6—Male deceased twin at 10 months.  
(G. Raap: Am. J. Roentgenol.)

connections are limited, namely, the epiphyseal area and the metaphyseal area close to the epiphyseal line. In these two areas, the reaction to complete or incomplete interruption of the blood supply is the same as in any area with limited anastomotic connections, and the process is known as aseptic necrosis. In these two areas are found the lesions so characteristic of decompression disease of bone. The favored seats for these lesions are the long bones, the shoulder joint

and the hip joint. The late effects of this process are recognizable roentgenographically. They are: (1) Aseptic necrosis of the hips and the shoulders; (2) medullary calcification in the diaphyseal ends of the long bones, and (3) hypertrophic arthritis. Not all of these need be present to justify the diagnosis. Asep-



Fig. 7—Femoral bone marrow 35 days after irradiation (1165 r). Marrow cellularity has returned to a level approximating the normal. Few fat vacuoles are evident and in this area there are 5 cegakarocytes.  $\times 350$ . (J. S. Barr, J. R. Lingley, and E. A. Gall: Am. J. Roentgenol.)

tic necrosis with osteoarthritis may occur without medullary calcification. Joint changes are more frequently present than changes in the long bones. The recognition of such bone changes is of paramount interest in time of war, as the incidence of symptoms due to decompression illness associated with high altitude bombing and fighting are on the increase."

**Comment**—Allan's work emphasizes the bone and joint changes attributable to nitrogen liberation in the tissues, dealing with increased activity in aviation. Bone and joint lesions due to nitrogen disturbances heretofore were associated



Fig. 8—Lower femoral epiphyseal plate in a normal untreated 30-day-old rat. Regular columns of active chondrocytes are arranged parallel with the long axis of the bone. Deposits of new bone may be seen along the lowermost portions of the cartilaginous trabeculae.  $\times 150$ . (J. S. Barr, J. R. Lingley, and E. A. Gall: *Am. J. Roentgenol.*)

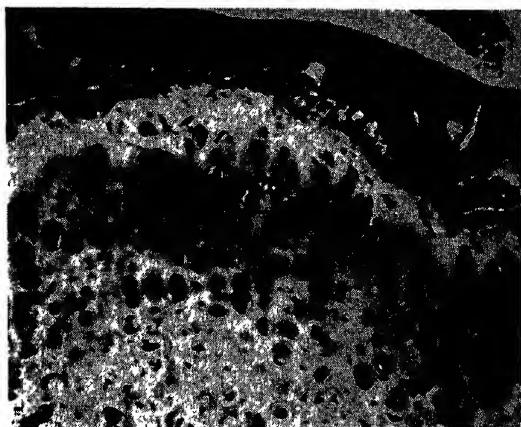


Fig. 9—Epiphyseal plate 14 days after irradiation (1165 r). Although the columnar structure persists, the columns are irregular and component chondrocytes are swollen and in many instances pyknotic. Cartilage matrix is mottled in appearance.  $\times 150$ . (J. S. Barr, J. R. Lingley, and E. A. Gall: *Am. J. Roentgenol.*)

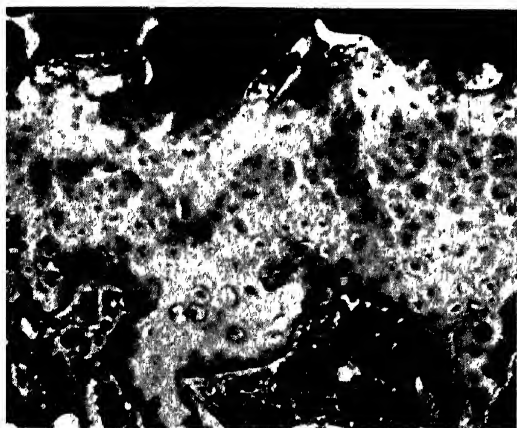


Fig. 10—Epiphyseal plate 184 days after irradiation (1165 r). Columnar arrangement is completely disrupted and cartilage cells are swollen and varied in size. A thin plate of bone has been deposited along the metaphyseal margin of the epiphysis and calcified cartilaginous trabeculae are no longer evident.  $\times 140$ . (J. S. Barr, J. R. Lingley, and E. A. Gall: *Am. J. Roentgenol.*)

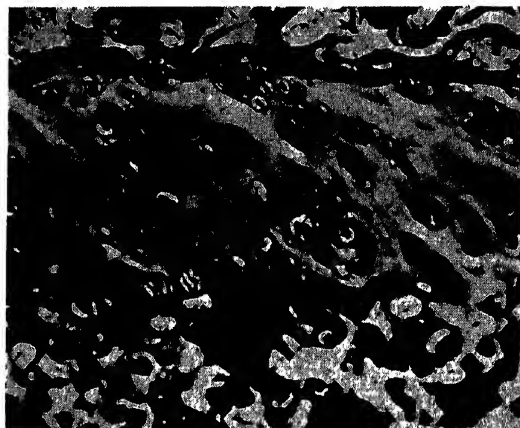


Fig. 11—Severely damaged epiphyseal plate 76 days after irradiation (1800 r). Chondrocytes are disarranged and obviously degenerated. The matrix is frayed and crumbly in appearance. A dark staining layer of sub-epiphyseal bone may be noted.  $\times 140$ . (J. S. Barr, J. R. Lingley, and E. A. Gall: *Am. J. Roentgenol.*)

primarily with caisson disease and observed in divers and tunnel workers.

**The Effect of Roentgen Irritation on the Epiphyseal Growth**—Barr, Lingley, and Gall<sup>4</sup> present results, histology, and roentgenographic studies on a group of 30-, 90-, 180-day albino rats. "The epiphyseal plate is a very radio-

sensitive tissue. Doses of 665 to 1165 r produced moderately severe histological changes, while doses of 1335 to 1800 r caused very severe disruption of the cartilage cell and destruction of the chondrocyte. There was no evidence indicating stimulation and only inconsequential evidence of regeneration of the epiphyseal



cartilage. Other tissues in the treated area, skin, subcutaneous tissue, muscle, synovia, and articular cartilage showed significant changes of transitory nature.

Degenerative or traumatic changes were noted in the treated joint (after nine months' observation). Careful measurement of the longitudinal growth of the tibia, after irritation, showed that the doses used (665 to 1800 r) all produced retardation of growth, and that the retardation varied proportionately to the irritation administered. The larger doses, 1335 to 1800 r, seemed to produce essentially complete arrest of growth of the treated epiphyses.

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## CHEMOTHERAPY

**Penicillin in the Treatment of Infections**—From observations based on a study of penicillin in 500 cases of infection, the authors<sup>5</sup> conclude that it is a remarkably potent antibacterial agent which can be given intravenously, intramuscularly, or topically. It is not efficient when given by mouth. It is excreted rapidly in the urine so that it is necessary to inject it continuously or at frequent intervals (three to four hours) in order to obtain an adequate amount of potent material in the blood and tissues. It has been found to be most effective in the treatment of staphylococcic, gonococcic, pneumococcic, and hemolytic streptococcus infections. It has been disappointing in the treatment of bacterial endocarditis. The average patient apparently requires a total of between 500,000 and 1,000,000 Oxford units and the best results have been observed when treatment is continued for at least ten days or two weeks, 10,000 units being given every two to three hours during treatment. Toxic effects are extremely rare; occasionally chills, headaches, and flushing of the face have

been noted. Urticaria has been reported and thrombophlebitis at the site of injection has been described.

**Comment**—The purpose of presenting this summary is to call attention to the developments concerning penicillin in relationship to bone and joint infections. Although no extensive reports are available on this subject, it is apparently quite certain that *penicillin* is well on its way to compete with or supplant *sulfonamides* in acute and possibly chronic infections of bones and joints (staphylococcic, streptococcic, pneumococcic, gonococcic). The Reviewer has had personal experience with two cases, one an acute multiple osteomyelitis in an infant and the second a chronic multiple osteomyelitis in a young adult, both of which are noteworthy in view of the fact that wound cultures following surgery were found to be sterile. Aside from saprophytes, such as *B<sub>1</sub> proteus* and *Staphylococcus albus* (nonpathogenic), the convalescence of these patients has been remarkably brief (wound healing by second intention two to four weeks and without complications).

## Sulfonamides

**Treatment of Hematogenous Osteomyelitis**—Thirty-one cases of acute osteomyelitis were treated by the authors.<sup>6</sup> *Surgical treatment* was employed in 27 in addition to *chemotherapy*. This was instituted when the clinical course and the physical signs indicated the presence of an abscess. The sulfonamide was administered on the basis of 0.1 Gm. (1.5 gr.) per pound of body weight each 24 hours and sulfathiazole was routinely used. The average dose for 21 of the patients was 4.6 Gm. (70 gr.) daily and was continued for an average of 11.7 days. The blood concentration was determined in 14 patients. The average blood level was



3.7 mg. per 100 cc. of blood. Six patients received *sulfapyridine* for an average of ten days at the average of 23 Gm. (6 dr.) per patient over this period. The blood concentration in this group averaged 4.1 mg. per 100 cc. of blood.

The authors' conclusions are as follows:

"1. Chemotherapy with sulfonamide drugs is a valuable addition to the treatment of acute hematogenous osteomyelitis in children, and should be used routinely.

"2. The greatest effect of the sulfonamides is on the infected blood stream, which is usually promptly sterilized.

"3. The incidence of death and of multiple bone involvement is reduced by routine sulfonamide therapy.

"4. In an occasional mild case of acute hematogenous osteomyelitis, the patient may recover by chemotherapy alone without surgery.

"5. Well-timed surgical drainage of abscesses and pyogenic granulomata is not supplanted by chemotherapy in the treatment of acute osteomyelitis, and should never be withheld from a patient on the false hope that recovery will result without drainage."

**Prevention and Treatment of Wound Infection**—Long<sup>7</sup> reviews the importance of sulfonamide compounds in the prevention and treatment of wound infection and brings our attention to the present status of these important drugs. "The use of sulfonamide compounds for oral and topical prophylaxis or treatment of contaminated or infected wounds is a valuable adjunct to careful surgical treatment but cannot replace it." On the basis of present evidence it would seem that a combination of systemic with local therapy offers the best chance for the prevention of wound infection and for its cure, once it has been established. On the basis of current evidence, *sulfa-*

*diazine* by mouth seems to be the drug of choice for systemic therapy and the doses of the drug should be adjusted so that concentrations of 4 to 7 mg. per 100 cc. are obtained in the blood. Higher concentrations are probably unnecessary. From all points of view, *sulfanilamide* seems to be the drug of choice for topical application. It is to be remembered that necrotic tissue and pus contain sulfonamide inhibitors and that every effort should be made to eliminate these inhibitors before sulfonamide is applied locally. Care should be taken to prevent the caking of sulfanilamide and this can be accomplished by applying *moist gauze dressings* following the application of sulfanilamide to the wound. In the absence of clinical infection, there is little reason to continue oral therapy with sulfadiazine for more than five to seven days. However, to prevent secondary infections from occurring after primary prophylaxis has been successful, it is necessary to apply sulfanilamide powder locally until the wound healing is complete.

## FRACTURES

**Compound Fractures**—Davis and Fortune<sup>8</sup> present an interesting study of compound wounds treated by what they term "a new conception in the treatment of compound wounds." It is their purpose to create at the time of compound injury, conditions which conform as nearly as possible to those in normal tissue. A thorough *débridement* under the most careful aseptic technic is step number one. This is followed by accurate *reduction of the fracture*, employing plaster and screws of vitallium or other nonelectrolytic metal for internal fixation, if needed. The wound is dusted with a layer of *sulfanilamide*. The wound is then closed with clips, woven silk, or chromic sutures; no tension su-

tures are permitted. If the skin defect is so large that closure without tension sutures is impossible, the flap is swung from a convenient side or both flaps are undermined or split, or a full thickness graft, depending on the area, is taken from the inside of the thigh and then

fixed. The last but most important is the very careful dressing after the manner necessary for skin grafting, whether or not a graft has been used. Figs. 12, 13, and 14 are illustrative. The authors point out four self-evident physical constants that are important in differentiat-

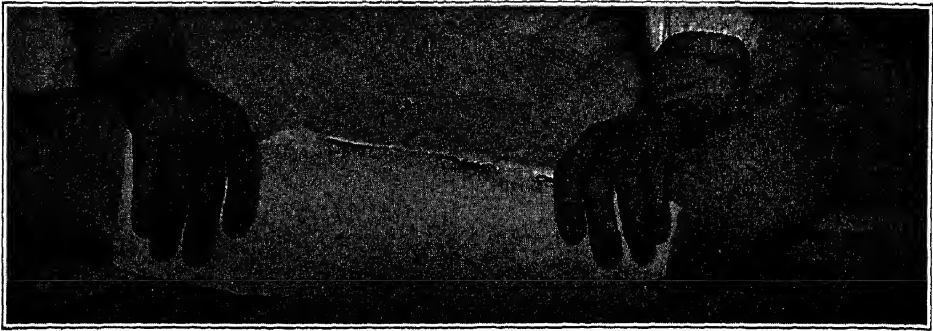


Fig. 12—Skin-fitting plaster slabs. (A. G. Davis and C. W. Fortune: J. Bone and Joint Surg.)



Fig. 13—Elastic pressure cone. (A. G. Davis and C. W. Fortune: J. Bone and Joint Surg.)



Fig. 14—The final plaster is placed over the preliminary pressure cone and extends from groin to toes. (A. G. Davis and C. W. Fortune: J. Bone and Joint Surg.)



Fig. 15—Pain was immediately relieved following transfexion. (R. Anderson, W. B. McKibben, and E. Burgess: J. Bone and Joint Surg.)

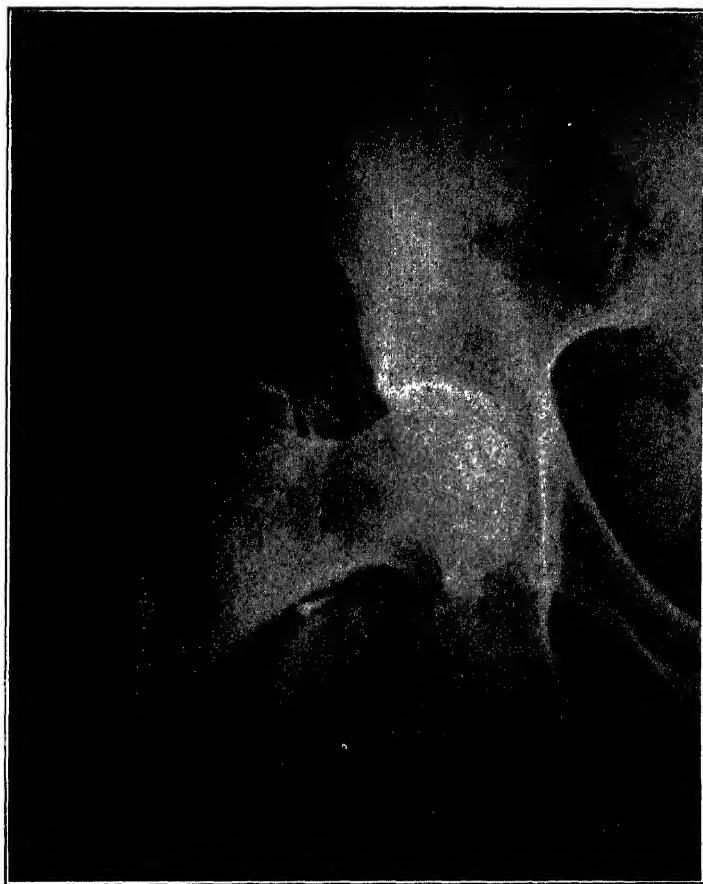


Fig. 16—Mrs. A. B., aged 93., Sept. 29, 1941. Note thinness of lateral side of trochanter. (R. Anderson, W. B. McKibben, and E. Burgess: J. Bone and Joint Surg.)



Fig. 17—Roentgenogram taken October 9, 1941. Overinserted pins can be withdrawn at any time.  
(R. Anderson, W. B. McKibben, and E. Burgess: J. Bone and Joint Surg.)

ing between therapy of surface and deep wounds.

#### DERMAL TISSUES

1. Are exposed to the chemistry and attenuated density of the atmosphere.
2. Exist in a dehydrating medium, with the relative humidity averaging between 20 and 50 per cent.
3. Are adapted to store ultraviolet radiation and to act as a filter to protect the deep tissues from such radiation.
4. The superficial layers are adapted to contact external objects.

#### DEEP TISSUES

1. Are exposed to the chemistry of plasma and the density of salt solution.
2. Exist in a fluid medium and are not subjected to dehydration.
3. The cells are not exposed to protein-coagulating ultraviolet rays.
4. Are not adapted to contact external objects. Cells and tissues are under sub-fascial pressure.

Accepting these essential differences in tissue demands, and applying what they term approved therapeutic adjuncts consistent with such demands, led to their approach. A total of 50 compound fractures that were treated with this technic are submitted.

Their conclusions are as follows:

"1. Fewer amputations, immediate and eventual, were necessary.

"2. There was an impressive reduction in sepsis.

"3. Nonunions were eliminated in this series.

"4. The number of delayed unions was reduced.

"5. The patients returned to their former occupations more often and more promptly.

"6. The prognosis was more certain.

"7. The scope of the types of compound injuries suitable for immediate primary closure was increased.

"8. Adverse postoperative complications and mortality decreased.

"9. There was a more perfect restoration of the function of muscle, tendon, skin, and bone."

the occupation of the individual, etc. Massive soft part damage, massive comminution as produced by an explosive shell, the inclusion of dirt from the battlefield, dirty clothing, and other foreign substances make this an unwise procedure for this type of wound. Obviously, the routine of the authors must be used in selected cases with full consideration



Fig. 18—December 22, 1941. Anteroposterior roentgenogram showing end result. (R. Anderson, W. B. McKibben, and E. Burgess: *J. Bone and Joint Surg.*)

**Comment**—The above routine stresses the importance of débridement, immobilization, topical sterilization (chemotherapy), and prevention of edema. The principles upon which this treatment is based are sound. Wounds, however, vary considerably with type of injury, the location at which they occur, and

being given to the possible type of contamination and the character of trauma, etc.

**Intertrochanteric Fractures: Non-operative, Castless, and Ambulatory Method of Treatment**—Anderson,<sup>9</sup> *et al.*, present a technic which depends upon a pencil-sized rod for immobiliza-

tion. It permits early crutch ambulation. Reduction is obtained on a fracture table and interfragment fixation is achieved by crossing three Steinman pins, the external ends of which are fastened to a dural rod. (Fig. 15.) Several beautifully reduced, difficult, comminuted,

Schneeberg<sup>10</sup> add additional cases to the 19 other cases of Milkman's syndrome found in literature. (Figs. 20, 21, and 22.) The authors' conclusions follow:

"1. Nineteen cases of multiple spontaneous idiopathic symmetrical fractures (the Milkman Syndrome) have been



Fig. 19—December 22, 1941. Lateral roentgenogram showing end result. (R. Anderson, W. B. McKibben, and E. Burgess: *J. Bone and Joint Surg.*)

trochanteric fractures are shown with splendid end result follow-up films. (Figs. 16, 17, 18, and 19.) According to the authors, the first advantage of this castless, nonoperative method lies in sufficient possible fixation that the patient may be fully dressed and ambulatory on crutches.

**Multiple Spontaneous Idiopathic Symmetrical Fractures**—Edeiken and

collected from the literature and a similar case has been added.

"2. The skeletal osteopathy of this condition is characterized by pain, disturbances of gait, and the radiologic appearance of spontaneous multiple symmetrical transparent bands or pseudo-fractures exhibiting little or no callus formation, which progress to render the victim bedfast.

"3. The disease appears mainly in middle-aged women.

"4. There are no distinctive laboratory findings.

"5. The etiology and pathogenesis are unknown. The syndrome may represent a variant or an atypical form of osteomalacia.

(19 lbs.), was free of pain, was ambulatory (her bizarre duck waddle gait persists), and is able to earn her living. Complete skeletal roentgenograms were repeated on April 5, 1943, and revealed excellent healing of all pseudofractures previously enumerated; no new lesions were noted.



Fig. 20—Lesions of forearms. (L. Edeiken and N. G. Schneeberg: J. A. M. A.)

"6. In the one case which came to autopsy, increased vascularity about the osseous lesions represented the sole distinctive pathologic change.

"7. Several reported cures have resulted from treatment with calcium, vitamin D, arsenicals, and vitamin A."

**Addendum**—After 25 weeks of therapy with 50,000 U. S. P. units of vitamin D orally and 3 Gm. (45 gr.) of calcium lactate daily, the patient gained 816 Kg.

**Comment**—The response to treatment in this particular case is strongly suggestive of a metabolic disturbance, closely related to vitamin D and calcium metabolism.

**Subastragalar Arthrodesis in Fractures of the Os Calcis**—Gallie<sup>11</sup> again revives the subastragalar arthrodesis as a means of combating some of the disabilities related to os calcis fractures. He includes pain through the joint on



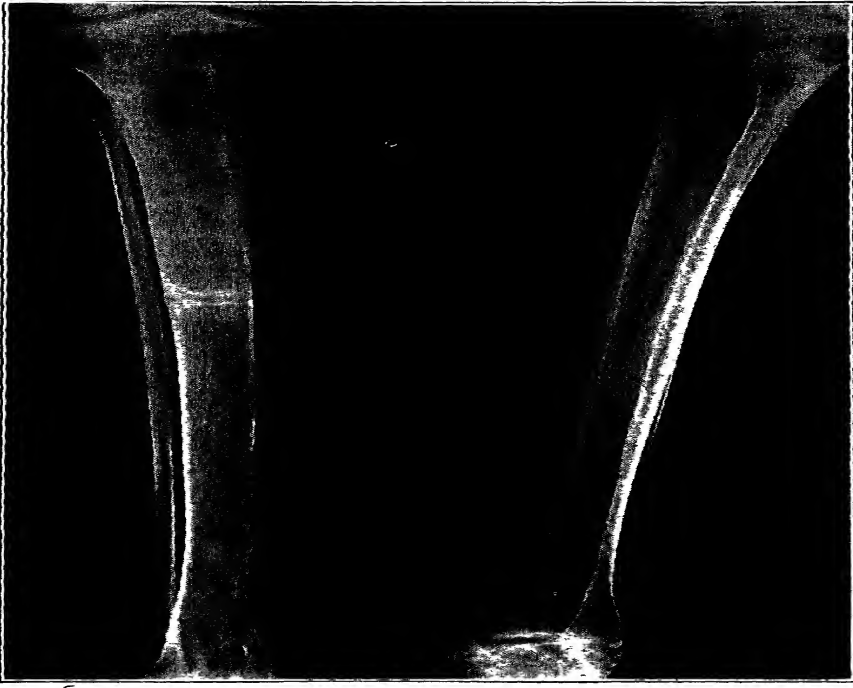


Fig. 21—Lesions in right tibia. (L. Edeiken and N. G. Schneeberg: J. A. M. A.)

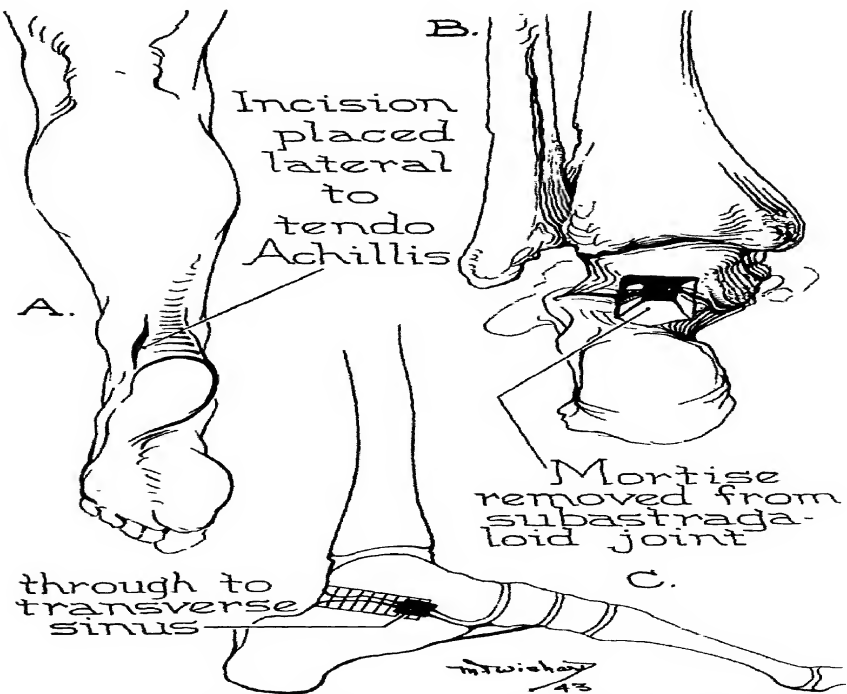


Fig. 23—Diagram illustrating arthrodesis of subastragalar joint. *A*, Incision lateral to tendo Achillis. *B*, View of skeleton from the back, showing the mortise cut in the astragalus and os calcis. *C*, Lateral view showing mortise extending through to the transverse sinus of the foot. (W. E. Gallie: J. Bone and Joint Surg.)

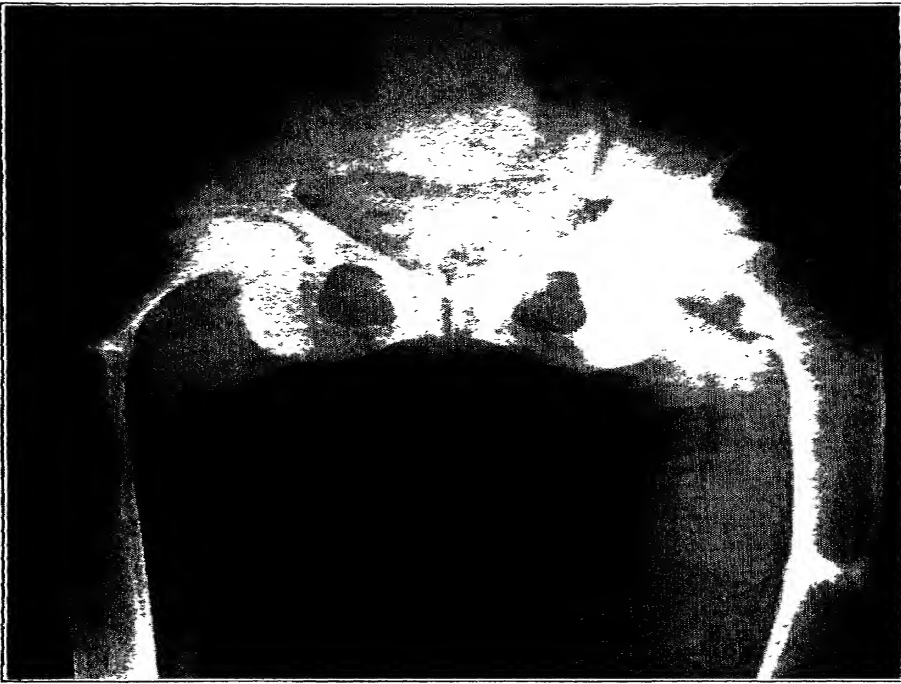


Fig. 22—Lesions in femurs (note heart-shaped pelvis). (L. Edeiken and N. G. Schneeberg: *J. A. M. A.*)

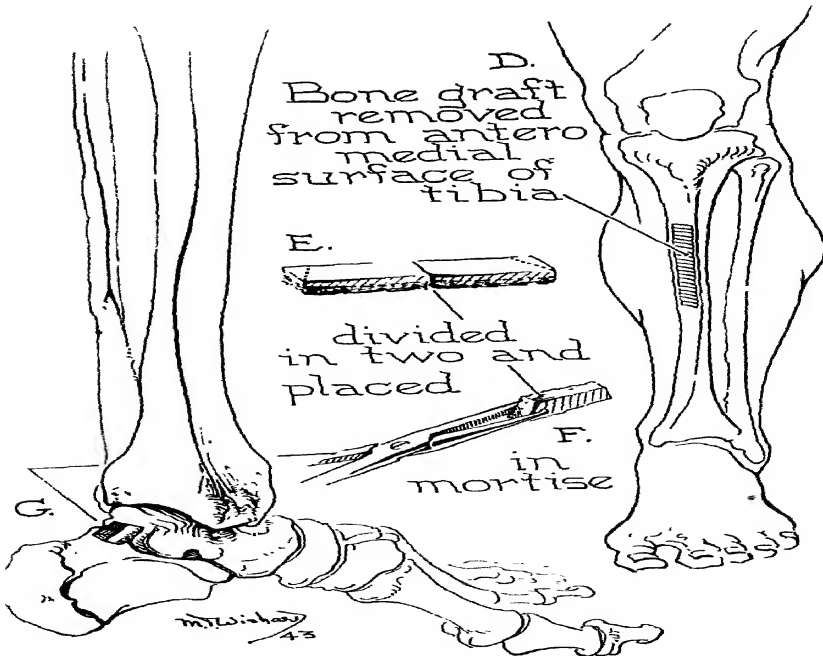


Fig. 24—D. A. graft  $2\frac{1}{2}$  inches long has been removed from the medial surface of the tibia. E, The graft has been bisected and bevelled as indicated by the dotted lines. F, The graft is ready for insertion into the mortise. G, One graft has been tapped into position in the mortise and the second is ready for insertion, completing the operation. (W. E. Gallie: *J. Bone and Joint Surg.*)



Fig. 25—Roentgenogram showing old fracture of the os calcis, involving the subastragalar joint in the sagittal plane, with half of the articular surface crushed down into the body of the bone. (W. E. Gallie: J. Bone and Joint Surg.)

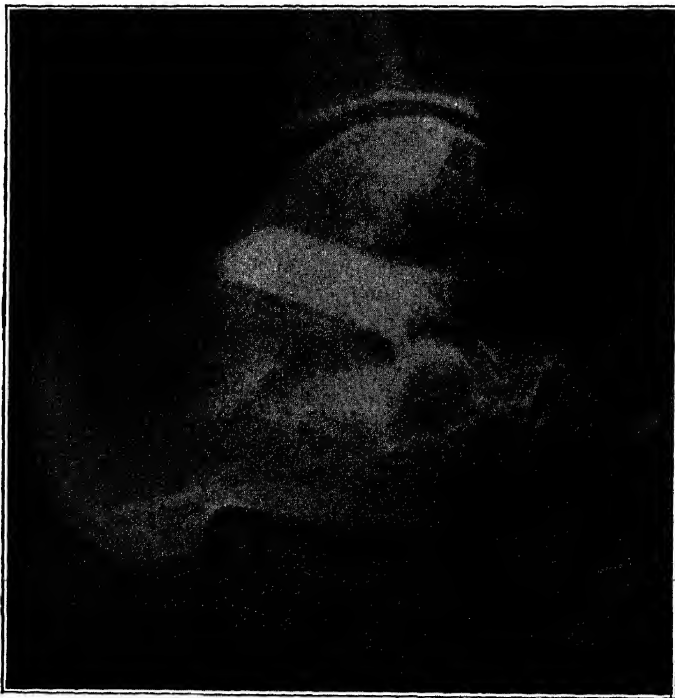


Fig. 26—Roentgenogram taken 3 months after operation, showing the grafts uniting to the walls of the mortise. (W. E. Gallie: J. Bone and Joint Surg.)



Fig. 27—Roentgenogram taken a year after the operation, showing solid arthrodesis.  
(W. E. Gallie: J. Bone and Joint Surg.)



Fig. 28—Preoperative roentgenogram showing the free body and apparent defect.  
(J. E. Milgram: J. Bone and Joint Surg.)



Fig. 29—Showing free body and joint surface. Note the cracks and avulsed lateral edge. (J. E. Milgram: *J. Bone and Joint Surg.*)



Fig. 30—Free body. Palisades are visible in lateral view. (J. E. Milgram: *J. Bone and Joint Surg.*)

walking or standing, acute twinges of pain when the heel strikes an uneven surface, marked limitation of the ordinary movements of the joint, and definite roentgenographic evidence of irregularity in the articulating surface. He proposes his own method of subastragalar arthro-

desis shown in Figs. 23, 24, 25, 26, and 27. The technic has been carefully worked out and has been employed for a period of six years.

His conclusions are based on a survey of 50 cases. In all, there has been primary union. In several cases in which the grafts were too loose, fusion was delayed and convalescence prolonged several months.

Conn, of Akron, Ohio, eight years prior to Gallie's article, proposed a triple arthrodesis in place of the subastragalar arthrodesis, calling attention to the fact that the astragaloscaphoid joint and the calcaneocuboid joint were usually deranged in os calcis fractures and believed that fusing the subastragalar joint alone in anything but the very simplest lesions was insufficient. The triple fusion operation has been more or less generally accepted throughout the country (astragaloscaphoid and calcaneocuboid and subastragalar fusion). Gallie's large series of cases, however, would indicate that both procedures are practical. Obviously, Gallie's operation should be confined strictly to subastragalar joint lesions.

**Tangential Osteochondral Fracture of the Patella**—Milgram<sup>12</sup> calls attention to another source of loose bodies in the knee which apparently occurs as a complication of lateral or inferior dislocation of the patella. Kroner in 1904 first reported a vertical frontal fracture of the patella in which the entire patella was split into two frontal sections. The patella was dislocated laterally and the fragment with the deeper cartilaginous surface remained laterally, while the remaining portion of the patella reduced itself. Villar, Kleinberg, Krida, Stewart, Leitloff, and Meekison reported cases of frontal or tangential fractures. The author reports four interesting cases in which the tangential fracture occurred. (Figs. 28, 29, and 30.) Operation is

indicated for the removal of the free body. Prompt surgery will minimize further trauma to the joint and will curtail the period of recovery and incapacity. A parapatellar incision is employed. In three of the operative cases, very definite injury to the external condyle of the femur was noted along with the fracture of the patella. The author believes trauma to be the principal etiological factor.

subtrochanteric fractures, osteotomies, nonunited fractures of the femoral neck, congenital dislocation of the hip, shortening of the femur, coxa vara, coxa plana, and for correction of vicious ankylosis.

### Internal Fixation of Metacarpal Fractures Exclusive of the Thumb—

The authors<sup>14</sup> present an analysis of 20 cases of metacarpal fractures in which

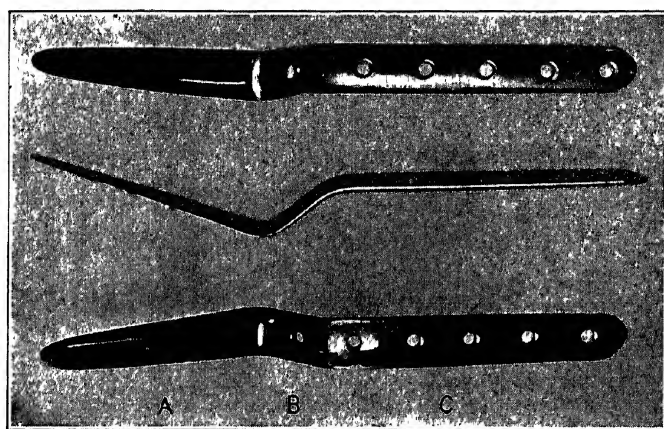


Fig. 31—Standard double-angle blade-plate for internal fixation of high femoral osteotomies. The angles and even the shape may be modified to suit the individual case. *A*, Blade; *B*, gooseneck; and *C*, plate. (W. P. Blount: *J. Bone and Joint Surg.*)

## FIXATION

**Blade-plate Internal Fixation for High Femoral Osteotomies—**The blade-plate is advocated by Blount<sup>13</sup> for fixation in high femoral osteotomies as well as fractures. Fig. 31 illustrates the blade and plate combination. Fig. 32 illustrates the application of the blade in this instance in conjunction with the Moore pin. The author's conclusions are as follows:

"1. A blade-plate is used for the internal fixation of high femoral osteotomies as well as fractures.

"2. The cast is eliminated.

"3. The patient may walk with crutches in less than two weeks." The rotation is accurately controlled. This type of fixation has been used in trochanteric and

the fractures had been reduced and fixation obtained by fixing the fractured metacarpal to an adjacent normal metacarpal with the aid of one or two Kirschner wires. In long oblique metacarpal fractures the bar may be passed through the fracture fragment as a means of fixation, or in the nonoblique type the wire is passed through the distal fragment and fixed to the adjacent metacarpal or metacarpals. The advantages are the free use of the hand, which is established immediately following reduction and fixation. It is the excellent fixation which prevents slipping.

**Comment—**The Reviewer has employed this method several times during the past year. The principal difficulties are in passing the Kirschner wire into the good metacarpal or metacarpals. These



Fig. 32—Anteroposterior roentgenogram of a combined trochanteric and subtrochanteric fracture with fixation with a single-angle blade-plate. Additional security was obtained with one Moore nail. The patient, a male, aged 59, walked with crutches after 10 days. (W. P. Blount: J. Bone and Joint Surg.)



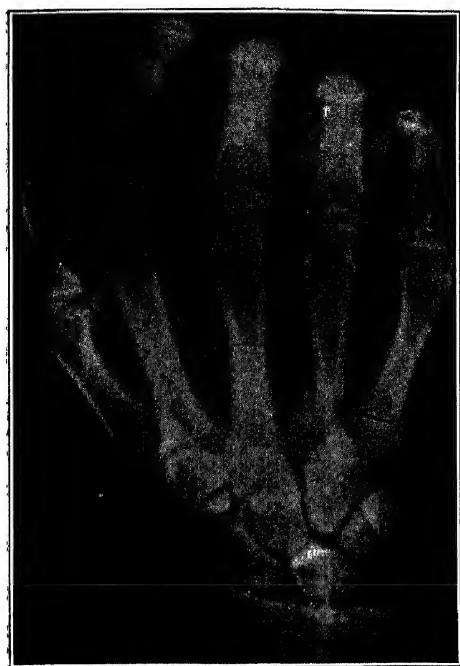
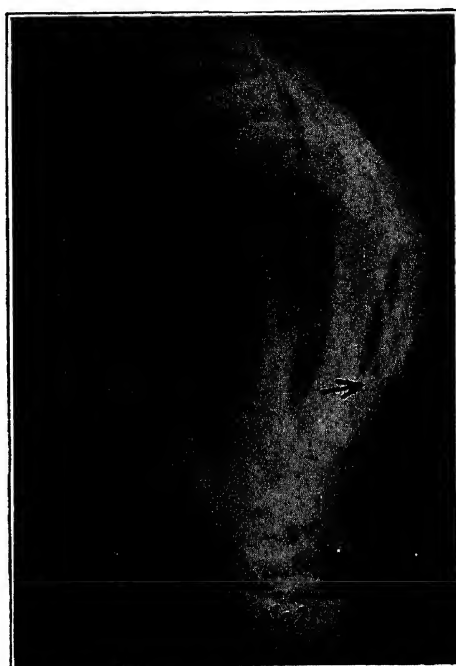
*A**B*

Fig. 33—Transverse fracture of the base of the fourth metacarpal, with shortening, displacement, and posterior angulation of the distal fragment. (E. F. Berkman and G. H. Miles: J. Bone and Joint Surg.)

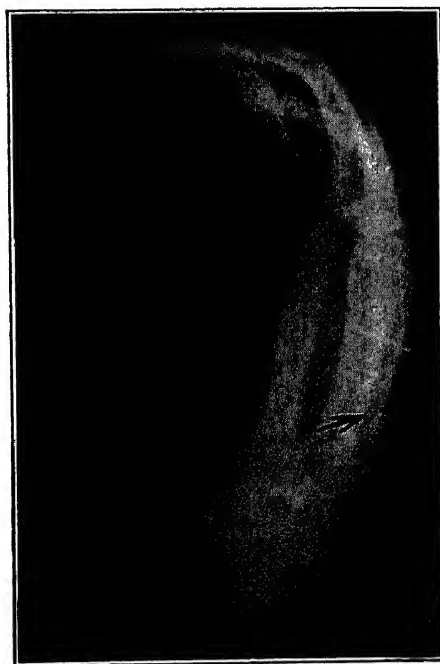
*A**B*

Fig. 34—The result following pinning. (E. F. Berkman and G. H. Miles: J. Bone and Joint Surg.)



*A* *B*  
 Fig. 35—Flexion and extension 1 hour after operation. (E. F. Berkman and G. H. Miles: J. Bone and Joint Surg.)

bones are small and even with the aid of a fluoroscope, it is hard to direct the wire properly. Figs. 33, *a* and *b*, 34, *a* and *b*, and 35, *a* and *b*, are illustrative.

**Migration of a Kirschner Wire from the Shoulder Region into the Lung**—Two instances of migration of

a Kirschner wire employed in the fixation of a glenohumeral arthrodesis and an acromioclavicular arthrodesis, respectively, are presented by Mazet.<sup>15</sup>

*Comment*—The dangers of wire, screw, and nail migration are well deserving of this emphasis.

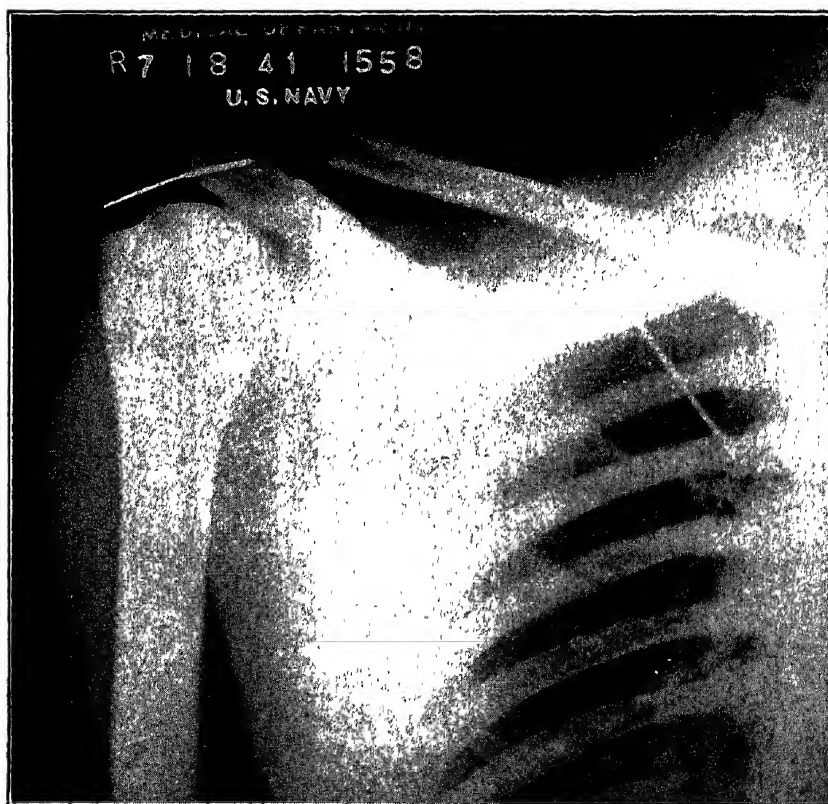


Fig. 36—Eleven weeks after the wiring, one wire is backing out through the deltoid and the other is in the right lung. The ligament is well calcified. (R. Mazet, Jr.: J. Bone and Joint Surg.)



Fig. 37—One wire is transversing the mediastinum and both lungs.  
(R. Mazet, Jr.: J. Bone and Joint Surg.)

**Plated Osteoperiosteal Graft—McBride<sup>16</sup>** reports 15 cases in which the plated osteoperiosteal bone graft was employed. Good union occurred in every instance. Union and restoration of function took place in three to six months. The plate was removed in six cases in 4 to 13 months after the operation. Figs. 38, 39, and 40 show the technic. Figs. 41 and 42 show the cases before and after treatment.

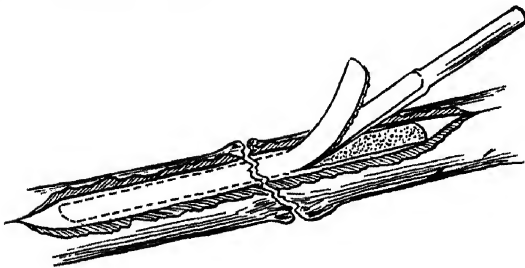


Fig. 38—Preparation of the host bed. The periosteum is incised and elevated sufficiently for the cortex to be flattened uniformly to the size of the graft. Intervening fibrous tissue and callus are not excised or disturbed except as absolutely necessary to restore alignment. (E. D. McBride: J. A. M. A.)

The author concludes that the metal plate is very dependable and that this simple procedure is more often justified in delayed union. It affords an early grafting operation in compound frac-

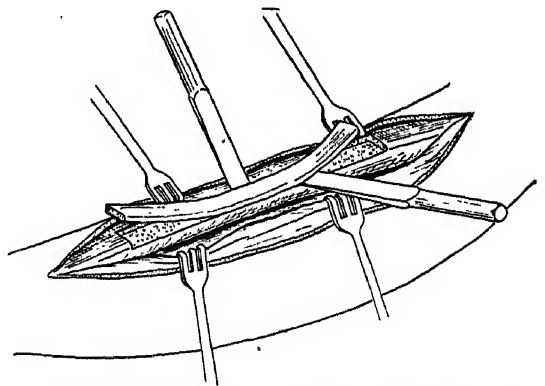


Fig. 39—Excision of graft. Removal of osteoperiosteal graft  $\frac{1}{8}$  inch thick from the crest of the tibia by retracting the muscles from the lateral margin of the tibia and starting the chisel or bone saw transversely  $\frac{1}{8}$  inch below the crest. The graft is first outlined on the anterior surface of the tibia, but is cut laterally from the crest rather than being chiseled out lengthwise, as is usually done. This is to prevent curling up of the graft and to insure uniform thickness. (E. D. McBride: J. A. M. A.)

tures with old scars and sinuses. It renders early passive motion. The resulting osteogenesis compares favorably with that obtained in full thickness grafts.

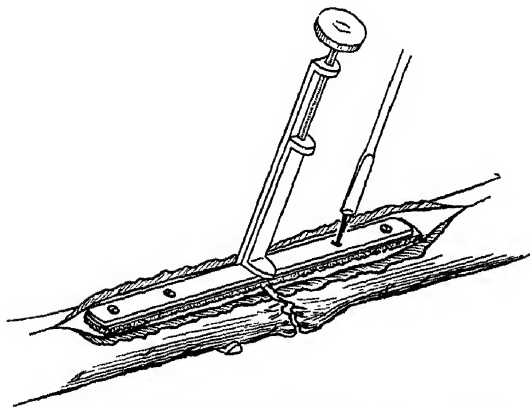


Fig. 40—Plating of graft on fragments. Application of the metal plate directly on top of the graft, in the customary method. The graft can be tied to the plate by catgut previous to application, since there is a tendency for the graft to slip about under the plate while the drill holes are being made. (E. D. McBride: J. A. M. A.)



Fig. 41—Before and after application of plated osteoperiosteal graft. This was a severely mutilated hand with persistent sinuses, still poorly healed at the time of operation. There was considerable loss of substance. A bone graft made it possible to obtain movement in the ankylosed wrist. (E. D. McBride: J. A. M. A.)

**Stabilization of the Articulation of the Greater Multangular and the First Metacarpal—Slocum<sup>17</sup>** presents an ingenious and sound stabilization procedure for metacarpal greater multangular dislocation. An incision is made over the dorsal lateral aspect of this joint, the dislocation reduced if present, and



Fig. 42—Three months after operation, showing consolidation of the ununited fracture. (E. D. McBride: J. A. M. A.)

part of the palmaris longus tendon obtained through another operative incision, is carried through the two bones as shown in Figs. 43, 44, 45a and b, which show the before and after follow-up status. This method of stabilization is comparable to that used in the shoulder by Nicolla; in fact, this is pointed out by the author and the point is well taken. It is suggested that the method might be employed in cases of old fracture dislocations and this is worth while considering.



Fig. 43—Roentgenogram showing dislocation at the articulation of the first metacarpal and the greater multangular. (D. B. Slocum: J. Bone and Joint Surg.)

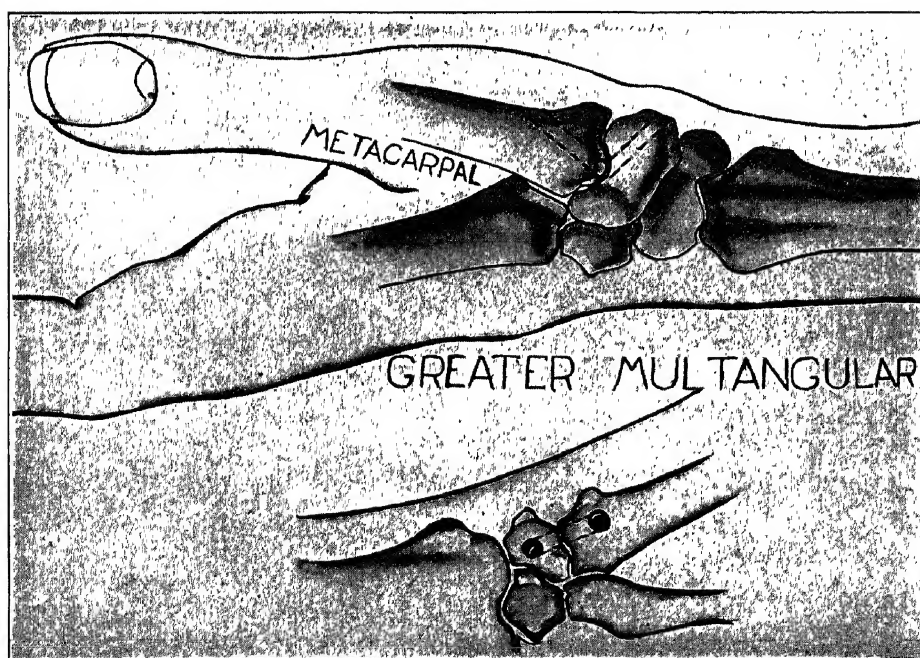


Fig. 44—Diagrammatic representation of placement of drill holes for the reception of the palmaris longus tendon. (D. B. Slocum: J. Bone and Joint Surg.)

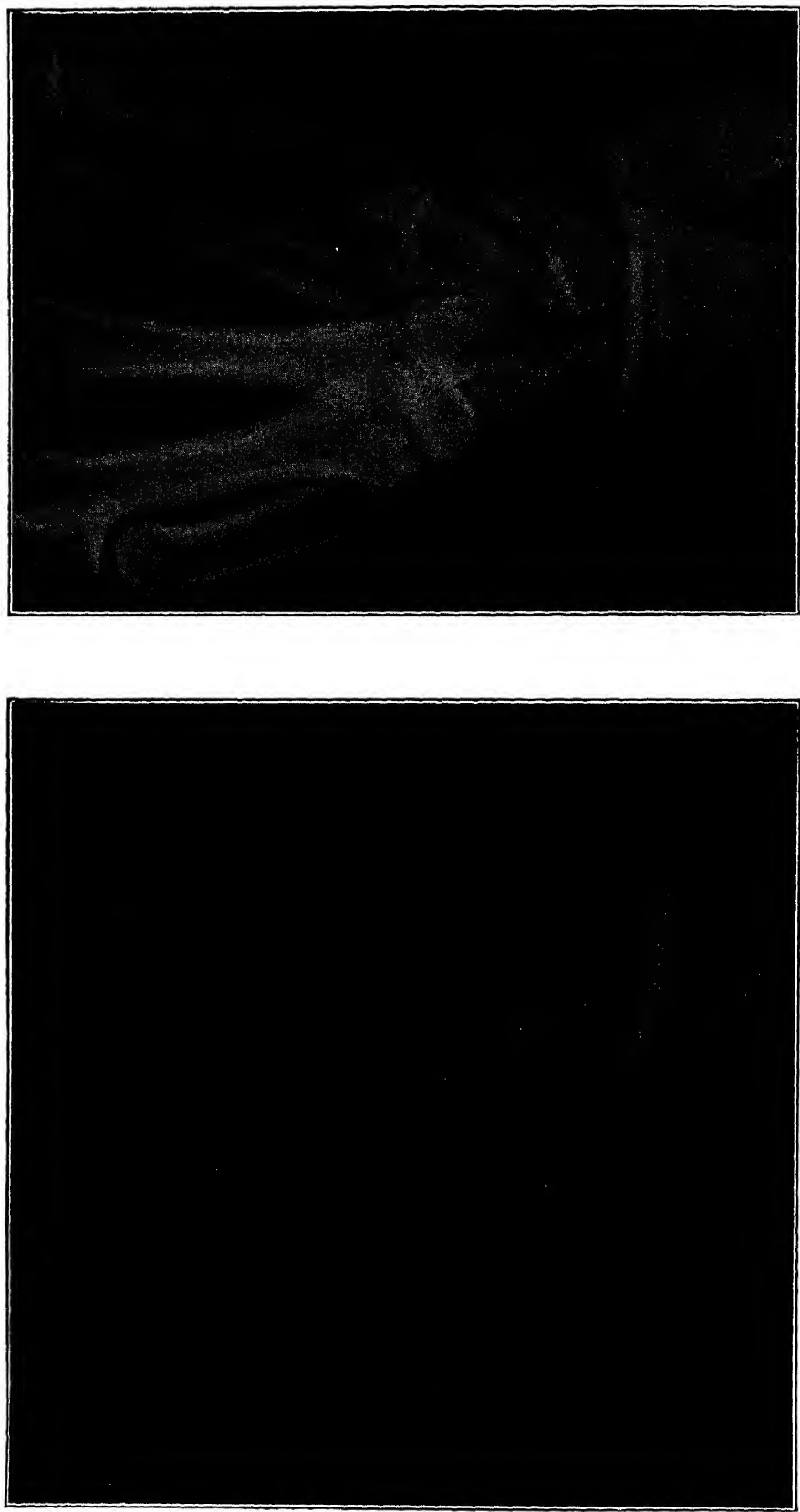


Fig. 45—Showing range of motion following stabilization. (D. B. Slocum: J. Bone and Joint Surg.)

## NONUNION

**Pin Distraction as the Cause of Nonunion**—Davis<sup>18</sup> presents six cases of nonunion, the cause of which has been traced to distraction. The author believes that a complete circular tear has occurred in the periosteum due to distraction. The osteogenic layer of the periosteum (cambium) and the insulation afforded by the periosteum have been lost as a result of the distraction tear. Figs. 46, *a*, *b*, *c*, *d*, and *e*, call attention to the importance of recognizing the distraction and emphatically warn against the general use of pin fixation, unless this principle is kept firmly in the foreground.

**Comment**—This timely contribution distinctly points out one of the principal causes of delayed and nonunion in pin fixation. With the advent of the Stader, Haines, Roger Anderson, and other pin fixation apparatus, an ideal method of perfect reduction, perfect fixation, and free joint movement seems to have arrived at last. However, nonunion has marred the splendid progress anticipated. Davis's presentation should be studied thoroughly by those interested in this type of fixation and his warning should be given ample consideration.

**The Bridging of Defects**—Boyd<sup>19</sup> presents a unique method of bone graft, the significance of which is thoroughly substantiated by his series of cases so well illustrated in this particular paper. The dual bone graft, Figs. 47 and 48, offers probably the most perfect mechanical fixation of any bone graft method presented to date. This graft was first employed in the treatment of congenital

pseudoarthrosis and uniquely successful repairs that occurred in these extremely discouraging fractures, offer first evidence of its efficiency.

Boyd reports a series of 22 nonunions, in which the dual grafts were used in 18. One failure occurred. One case could not be traced and three have been operated upon too recently to determine the end result. In the remaining four cases, massive fibular grafts were employed. The remaining cases were entirely successful. Figs. 49, 50, 51, and 52 are typical of the splendid results shown.

***Technic of the Dual Bone Graft***—

The ends of the pseudoarthrosis fragments are freshened and the sclerotic bone at the ends excised. The medullary canal in each fragment is thoroughly opened with a drill or curetted. The pseudoarthrosis is then reduced and the fragments are held in optimal position. The sides of the fragments have been denuded and flattened to receive the grafts. A long graft is removed from the anterior medial surface of the opposite tibia. The periosteum is not removed with the graft. The cancellous portion of the graft is removed with the motor saw. Two cortical grafts are obtained by dividing the graft in the center and they are then placed in their respective beds previously prepared in the pseudoarthrosis fragments. Fixation is obtained by screws passed through from one graft to the other, piercing the enclosed fragments. The cancellous bone is packed into the crevices and *sulfanilamide* powder is dusted into the wound.





Fig. 46—Nonunion. *A*, Day of accident. *B*, Pin traction introduced 6 days later. *C*, Status 13 weeks later. *D*, Nonunion demonstrated and operation performed 5 weeks later. *E*, Six months after bone graft. (A. G. Davis: J. Bone and Joint Surg.)



Fig. 47—Typical congenital pseudoarthrosis in a child aged 5 years. (H. B. Boyd: J. Bone and Joint Surg.)



Fig. 48—Appearance of the bone immediately following the application of the dual bone graft. Note the proximity of the grafts to the lower epiphyseal line. (H. B. Boyd: J. Bone and Joint Surg.)



Fig. 49—Nonunion of the radius as first seen at the clinic 16 months following compound fracture which had been treated by open reduction and internal fixation. (H. B. Brown: J. Bone and Joint Surg.)

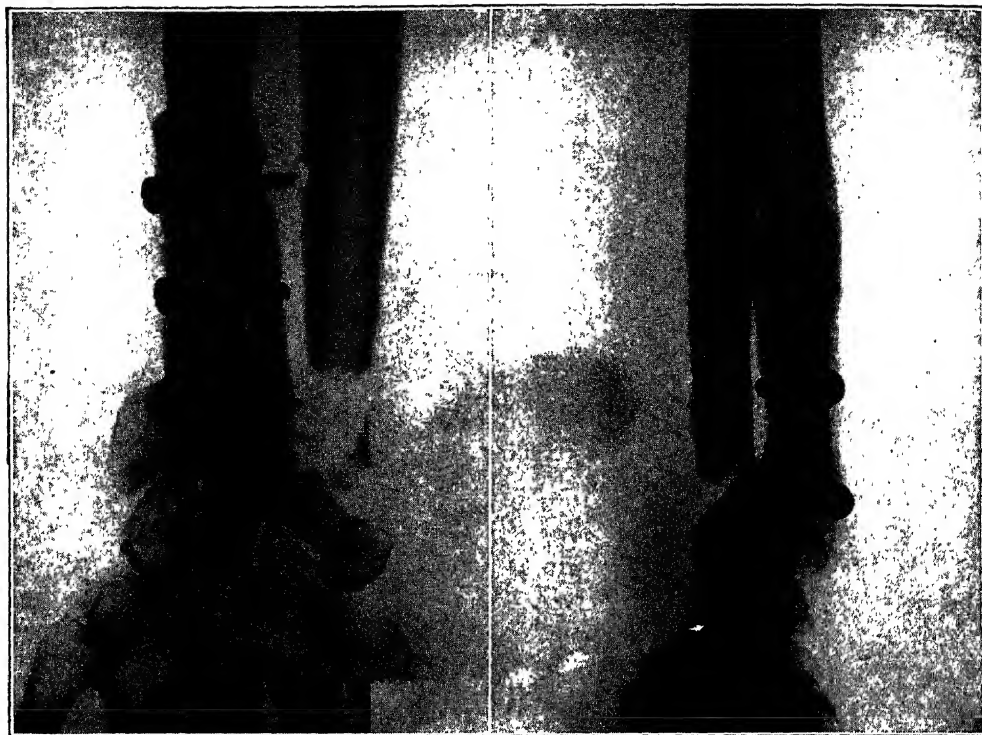


Fig. 50—Appearance of the radius 9 months following application of dual bone grafts. This illustrates the forcepslike action of the dual graft on the small osteoporotic fragment. (H. B. Boyd: J. Bone and Joint Surg.)

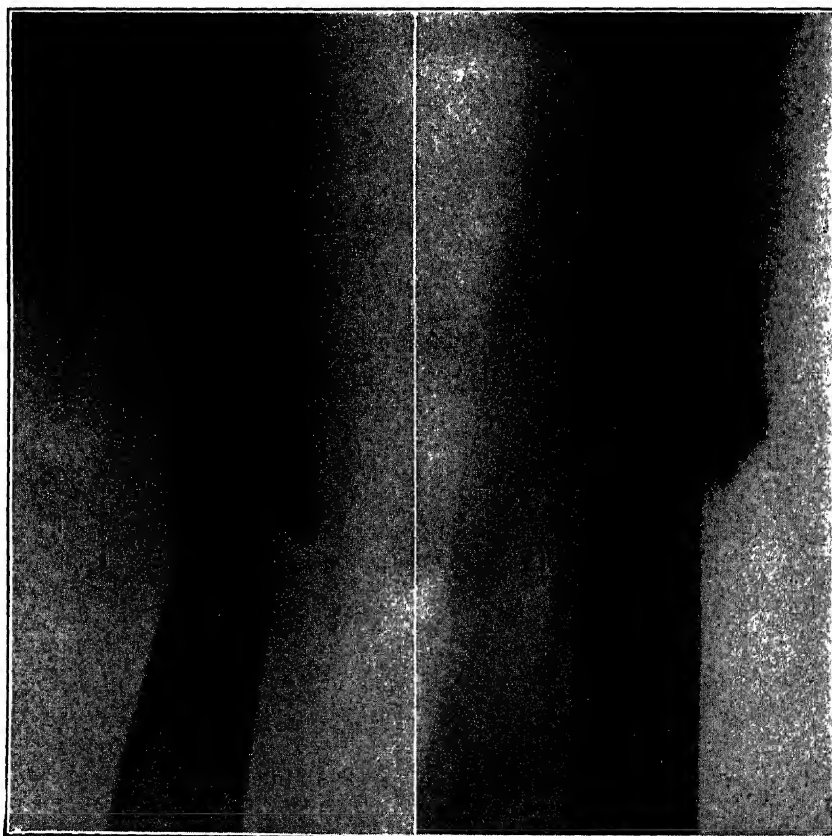


Fig. 51—Nonunion of the femur, of 2 years' duration, followed a compound fracture and sequestration. (H. B. Boyd: J. Bone and Joint Surg.)



Fig. 52—Condition of the bone 4 months following application of dual bone graft. It is too early to state whether a solid bony union will occur. However, the wound healed without infection and the patient is walking in a brace. (H. B. Boyd: J. Bone and Joint Surg.)

## MALFORMATIONS

### Malformations of the Extremities

—Congenital malformations are induced in rats<sup>20</sup> by maternal nutritional deficiency. These malformations have their incipency in the cartilaginous or precartilaginous stage of the structures affected. The defects of ossification are a secondary result caused by the faulty development of the precursors of bone. Many cartilaginous structures show a lack of division in the longitudinal and transverse direction. This leads to a reduction in the number of skeletal elements and to syndactylism, and brachydactylism in the paws. The radius, ulna, tibia, and fibula are frequently shortened in the cartilaginous stage. Ossification is delayed and faulty and eccentric centers

of ossification lead to abnormal arrangement of the bone trabeculae.

At the age of four weeks, female albino rats were placed on a rachitogenic diet and were supplied with viosterol to prevent the development of rickets. The females reared on this diet were retarded in growth and maturation and were, as a rule, not mated until the fifth or sixth month. At this age, successful matings took place frequently, although their pregnancies were not always carried through. A number of females were resorbing their fetuses at this stage of development. Of 59 females reared and bred on this diet, 48 of the offsprings were obtained; 39.5 per cent were abnormal. The abnormal newborns could be recognized by external inspection. A

receding mandible and a protruding tongue as well as various abnormalities of the extremities could be seen externally. Fusion of the fifth to the eighth ribs, premature fusion of the centers of ossification of the sternum were observed after clearing and staining. Shortening to the absence of the radius, ulna, tibia,

cause of various congenital malformations in pigs, calves, and rats. Byerly, Titus, Ellis, and Landauer described micromelia of chick embryos caused by nutritional deficiency of laying hens. The work of Warkany and Nelson adds further to our knowledge of the teratogenic environmental factors and it

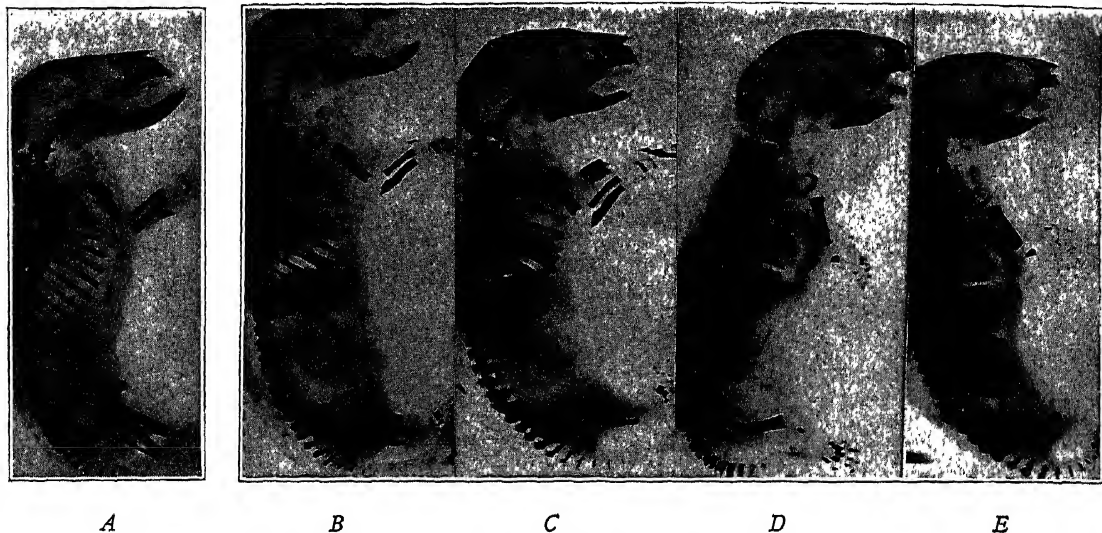


Fig. 53 *A*, Cleared specimen of normal newborn rat. *B-E*, Cleared specimens of abnormal newborn rats, showing shortening of mandible; shortening or absence of radius, ulna, tibia, and fibula; and fusion of ribs. (J. Warkany, R. C. Nelson, and E. Schraffenberger: *J. Bone and Joint Surg.*)

fibula, metacarpals, and phalanges, became recognizable. The flat bones of the skull and those of the vertebral column were not grossly affected. (Fig. 53, *a, b, c, d*, and *e*.)

**Comment**—The authors call attention to the fact that our interest in congenital malformations has been centered largely about the genetic factors leading to these malformations while the environmental and the teratogenic factors have somewhat lagged behind. However, they point out that Franke and Tully have described malformations in chick embryos whose mothers were fed grains containing selenium. Experiments by Hale, Moore, Huffman, Duncan, and Anderson pointed to the lack of vitamin A in the maternal diet as a possible

would seem that these remarkable, beautifully controlled, and convincing experiments are perhaps on the verge of offering not only an explanation for certain types of congenital malformations but also possibly prevention and treatment.

**Etiology of the Undescended Scapula and Related Syndromes**—In contrast to the mechanistic views, the “bleb theory” explains the peculiarities of the undescended scapula and furthermore brings it into closer relationship with other syndromes to be mentioned later. The “bleb theory” briefly is as follows: “If for some pathological reasons, such as an excessive production of cerebral spinal fluid or its deficient reabsorption—or perhaps in consequence of a primary dysunion in the midline, the area



membranacea remains unduly patent, cerebrospinal fluid escapes into the subcutis of the adjacent neck region. The blebs so formed spread on the body surface and on their path exert a deleterious influence by pressure and provoke an inflammatory reaction. They are driven by physical forces toward areas of least resistance and are arrested and retained by preformed cavities and pockets, like the orbits or limb buds."

It has been shown experimentally by Bagg, Little, and Bennevie that these blebs are the true cause of manifold deformities in animals, such as clubfoot, clawhand, and polydactylism. These deformities were obtained in the progeny of mice whose ovaries were submitted to irradiation. Blebs were also observed in human embryos and associated with anomalies of the fingers and toes (Bonnievie). The author<sup>21</sup> shows that bleb formation, which he considers responsible for the undescended scapula, occurs in the fifth to sixth embryonic week. At that period the shoulder blade is still at the level of the fourth cervical to the first thoracic vertebrae. This also is the time when the upper limb buds appear. The distance of the limb bud from the neck region during the fifth to sixth embryonic weeks is only a few millimeters so that a combination of anomalies of the scapula and the upper extremity is understandable. Ingalls believes that Sprengel's deformity, Klippel-Feil syndrome, and symbrachydactylia belong to the bleb diseases.

## PARALYSIS

**Spastic Paralysis and Allied Disorders**—In a series of 1720 consecutive cases, the authors<sup>22</sup> analyze carefully the various types of spastic paralysis. In 1217 cases in which the pathology was in the pyramidal tract, surgical

treatment has been discussed in detail. The total number of operations on the upper extremities was 115 with only 16 good results. Surgical treatment on the whole is unsatisfactory, with improvement primarily cosmetic and not functional. Surgery seems permissible in attempts to improve pronation at the forearm and flexion deformity at the wrist. In the lower extremities there were 1063 operations with 677 considered good results. Surgical treatment on the whole was regarded satisfactory but should be restricted to correction of adduction deformities of the thighs, internal rotation deformities of the thighs, flexion deformities of the knees, spasm or contracture of the heel cord, and other fixed foot deformities.

**Full Active Abduction in Traumatic Paralysis of the Deltoid**—Staples and Watkins<sup>23</sup> present two

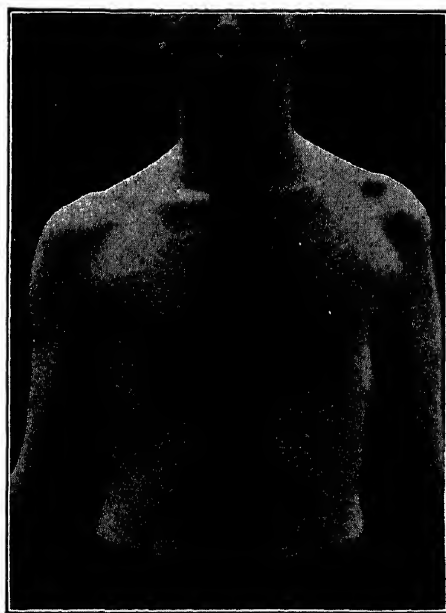


Fig. 54—Paralysis of left deltoid muscle of 6 months' duration. O. S. Staples and A. L. Watkins: J. Bone and Joint Surg.)

cases of isolated paralysis of the deltoid in which all movements of the shoulder were normal with the exception of posterior flexion. It is their impression

that, providing there is normal strength in the other shoulder girdle muscles, full active abduction can be effected as has been illustrated by the two patients with

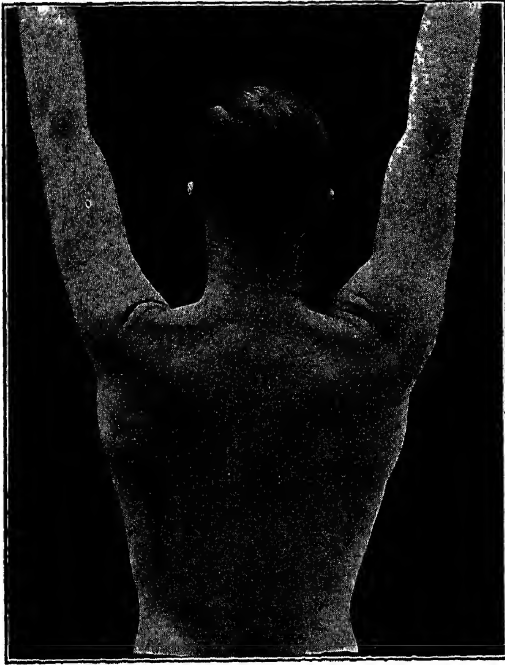


Fig. 55—Full abduction is essentially equal on the 2 sides. (O. S. Staples and A. L. Watkins: *J. Bone and Joint Surg.*)

traumatic deltoid paralysis. Figs. 54, 55, and 56 are illustrative. Both were traumatic in origin.

### POLIOMYELITIS

**Poliomyelitis and Pregnancy**—The authors<sup>24</sup> present personal studies of

two cases of poliomyelitis complicating the latter part of pregnancy. They tend to show that poliomyelitis in the mother has no effect on the fetus (fetal poliomyelitis) nor does it influence the course of pregnancy in the paralyzed mother. The literature is reviewed and it is pointed out that a number of other virus diseases, such as influenza, encephalitis, lymphocytic choriomeningitis, and probably the virus of measles and of chicken-pox, regularly pass through the placenta and congenitally affect the fetus. The fact that the virus of poliomyelitis does not congenitally affect the fetus is explained as due to the fact that the virus of poliomyelitis does not enter the blood stream. The work of Brahdly and Lenarsky and that of Kleinberg and Horwitz offers further confirmatory evidence to their conclusions.

Kleinberg and Horwitz reviewed a total of 29 cases of poliomyelitis complicating pregnancy in which a normal child was obtained in 24 incidences (22.8 per cent). Four of the cases that were stillborn or had an early fetal death were associated with prematurity and there was no evidence of poliomyelitis in any of this group. Harmon and Hoyne report two cases. Case one, a

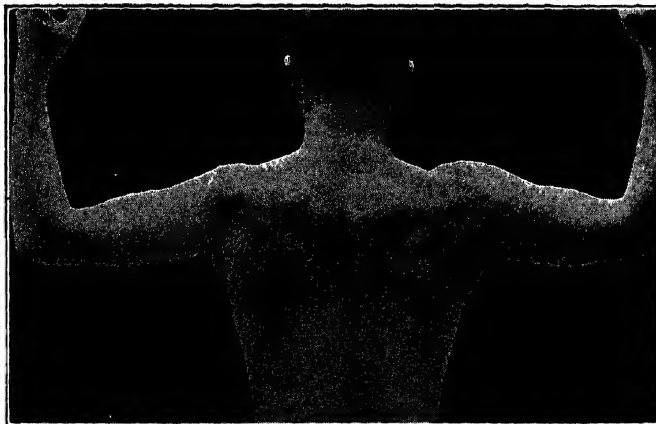


Fig. 56—Abduction in external rotation with normal relation of the humerus and the scapula. The left shoulder in abduction is almost as strong as the right. (O. S. Staples and A. L. Watkins: *J. Bone and Joint Surg.*)



30-year-old woman, six months pregnant, dyspneic, cyanotic, abdominal and accessory respirations, alae nasi dilatation upon inspiration, exhausted and with partial paralysis of the left upper extremity, offered the material for their first case. Spinal fluid study plus the clinical picture confirmed the diagnosis of poliomyelitis. A stillborn fetus was delivered on the tenth day after admission. The mother made an uneventful recovery except for the residual paralysis in the left upper extremity. Intracerebral inoculation of a *Macacus rhesus* monkey with supernatant fluid from the ground emulsion of 0.3 Gm. of the fetal spinal cord was performed after preservation of the cord at 5° C. for 40 days in 50 per cent glycerin. The animal showed no signs of poliomyelitis clinically or on autopsy on the twenty-sixth day. Fetal death in this case was described by the authors as due to maternal and fetal anoxia.

Case two was a 32-year-old woman, eight months pregnant, with bulbar poliomyelitis. A residual paralysis was noted in the muscles of the right shoulder girdle and the entire right lower extremity. Labor was induced and a normal viable child resulted. Follow-up ten months after birth showed a normal child without any apparent evidence of poliomyelitis.

**The Results of Poliomyelitis in Baltimore**—This report<sup>25</sup> is a study of the results of a poliomyelitis epidemic in Baltimore in 1941. In this report is also a study of cases of poliomyelitis treated in previous years and observed for the degree and rapidity of recovery of specific muscles. In the 1914 epidemic, there were 296 cases, an incidence of 16.3 per 100,000 population. There were nine deaths. All the cases were reviewed in 1942. The author's conclu-

sions were as follows: In the 1941 epidemic in Maryland, 68 per cent of the patients recovered and 14 per cent more had a slight residual weakness. Only 2 per cent had a complete disability. The treatment consisted of protective care and physiotherapy for the weak muscles. There was no complete immobilization of the patient or of the extremities. The patients who do not recover rapidly or spontaneously need prolonged treatment in an effort to bring weak muscles to their maximum power. Muscles do not improve in direct ratio to the initial weakness and may continue to improve for 18 months in those cases treated immediately after the onset of the poliomyelitis. Patients in whom treatment has been at a later date may continue to improve for an average period of nine months.

**Comment** — The figure indicating complete recovery, namely 68 per cent, does not compare favorably with the present claims of the exponents of the Kenny Treatment. This again shows the difficulty in comparing statistics in cases of epidemics, there being two illusive factors that always tend to interfere with comparisons. These two factors are the virulence of the virus and the resistance of the host.

**Prostigmine in Treatment**—Kabat and Knapp<sup>26</sup> are of the impression that muscle spasm in poliomyelitis is closely related to the damage of the internuncial cells of the spinal cord by the virus of poliomyelitis. Internuncial lesion interferes with and disorganizes synaptic transmission to the anterior horn cells and the muscular hypertonus and proprioceptive reflex hyperirritability (authors' concept of muscle spasm) are considered release phenomena resulting from the removal of inhibition of anterior

horn cells due to synaptic disorganization. Prostigmine and physostigmine are known to depress the function of an enzyme called cholinesterase. By inhibiting cholinesterase, prostigmine allows acetylcholine to accumulate to a greater extent than normal at synapses, parasympathetic nerve endings, and myoneural junctions and in the blood and in that way produces profound physiologic changes throughout the body. The effects of prostigmine on muscle function in poliomyelitis have been studied in a series of 24 patients ranging from two to six years of age. *Prostigmine* was administered as follows: Treatment was begun by studying the effects of hypodermic injections of prostigmine. The prognosis could be estimated roughly by the improvement resulting from a single subcutaneous injection. The dosage is as follows: Adult 1.5 to 2 mg. of prostigmine methylsulfate; children, 8 to 13 years, 1 mg. prostigmine with or without 0.0003 Gm. ( $\frac{1}{200}$  gr.) of *atropine*; children, 2 to 6 years, 0.5 mg. of prostigmine without atropine. With these doses, beneficial effects on muscle spasm were observed with no serious toxic symptoms. Oral administration of prostigmine followed, provided there had been any prompt release of muscle spasm (within one hour) by the above test dose. For adults, the usual dose was gradually built up to prostigmine bromide, 45 mg., and atropine sulfate, 0.00065 Gm. ( $\frac{1}{100}$  gr.) three times a day. Smaller doses were employed for children and infants. The dosage usually caused no toxic or unpleasant symptoms provided the prostigmine and atropine are carefully balanced. The patients have taken these doses for two months. The changes in muscle spasm were determined by the goniometer. The range of motion of the muscle group were recorded in this manner.

The authors' conclusions are:

"1. Prostigmine decreases skeletal muscle hypertonus and proprioceptive reflex hyperirritability ('muscle spasm') in patients with poliomyelitis. It also reduces 'inco-ordination.' These effects may be evident one hour after subcutaneous administration of the drug. These actions of prostigmine apparently depend on alteration of function of synapses in the spinal cord and are not antagonized by atropine.

"2. Prostigmine has been given a preliminary trial as an adjunct in the treatment of poliomyelitis. The approach to therapy has been based on the Kenny concept of the disease. In a series of 20 patients, most results have been encouraging. The drug significantly increased the range of passive motion, decreased or eliminated deformities in some instances by relaxation of hypertonus, and in some cases improved active motion. In a number of instances, muscle spasm has shown more rapid improvement when prostigmine was added to the Kenny routine. In a majority of cases, the drug appeared to accelerate recovery."

Incidentally, Kabat has been able to produce localized lesions of the internuncial neuron in dogs and has produced hypertonus of the skeletal muscles similar to that observed in clinical poliomyelitis.

**Comment**—Kabat and Knapp have contributed an interesting approach to the problem of muscle spasm. It is obligatory that the evaluation of this paper be restricted largely to the physiologists. From a purely clinical point of view, one is not impressed with the value of prostigmine as a therapeutic agent at this time. Further studies and observations may add to our present knowledge.

## ROENTGEN THERAPY

**Metastatic Malignancy of the Spine**—Toumey<sup>27</sup> reports a study of 95 cases of metastatic malignancy of the spine. The symptoms were astonishingly variable. Back pain was the most common symptom. Other complaints were also listed: weakness of the legs, retention of the urine, paraplegia, hip pain, sciatica, and loss of weight. Carcinoma of the breast, carcinoma—site unknown, carcinoma of the prostate, Hodgkin's disease, carcinoma of the thyroid, plasma cell myeloma, adenocarcinoma of the uterus, and carcinoma of the bladder were the principal sources of the malignancy.

The author's conclusions are as follows:

"1. Roentgenograms of the spine should be taken in all cases of persistent back pain, even when the symptoms are mild. If the clinical diagnosis of spinal metastasis is made, roentgenotherapy should be employed, even if roentgenograms are negative.

"2. *Roentgenotherapy* is the most valuable means at our disposal for relief of pain in metastatic malignancy of the spine.

"3. The results achieved with *cobra venom* have been disappointing.

"4. For intractable pain in the low back, lower extremities, and pelvis, *subarachnoid injection of alcohol* is useful, although there is the risk of injury to the spinal cord.

"5. *Chordotomy* is the method of choice for patients whose general condition and prognosis for length of life warrant a surgical procedure. The results are more certain and satisfactory than those obtained by subarachnoid injection of alcohol.

"6. *Orchectomy* is of value in carcinoma of the prostate because of the clinical

improvement in cases so treated. It is as yet too early to report the end results of this treatment.

"7. *Salicylates* and *codeine* were used in the earlier stages, and *dilaudid* was preferred in the later stages for the control of pain. Chronic back pain unrelieved by recumbency, salicylates, and codeine is usually the pain of cancer.

"8. *Braces* help relieve back pain in some patients with vertebral compression."

**Acute Subdeltoid Bursitis**—Brewer and Zink<sup>28</sup> strongly urge the employment of *x-ray therapy* in the treatment of acute subdeltoid bursitis and report 11 out of 14 cases having a disability of less than 48 hours following this type of therapy. They urge a trial of this type of therapy in chronic subdeltoid bursitis. The dosage for acute cases consisted of a single treatment of 300 roentgens. Occasionally it was repeated in seven to ten days. A typical response in an acute case is a frequent but not inevitable aggravation of symptoms in 8 to 24 hours. Adequate analgesia must be provided during this period. The short period of aggravation is followed by rapid relief of pain and restriction of motion. A residual tenderness usually disappears in a few days and the calcium deposits will be absent in many instances. "If roentgenograms are repeated in a few weeks, the result is often quite startling both to patient and to referring physician."

**Comment**—The effects of roentgen therapy on subdeltoid bursitis (acute) has been very unsatisfactory in the reviewer's experience. It is highly probable that sufficient roentgen dosage was not employed. This rather conclusive work of Brewer and Zink should revive interest in this form of therapy.

**Gas Gangrene**—"McMilan<sup>29</sup> collected from the literature 416 cases of

gas gangrene in which roentgen therapy was used and reports 13 new cases in which this treatment was employed. Roentgenograms should be taken of the involved area every four to six hours in injuries where gas gangrene is liable to develop. This will lead to an early diagnosis. The development of clinical signs

the antiserum if the infection is more than 12 hours old or if the patient does not respond clinically to the foregoing treatment. Amputation should not be resorted to for gas gangrene *per se*. Of the 416 patients given x-ray treatment 62 died, giving a mortality of 14.0 per cent. Millar's review of 607 cases before the

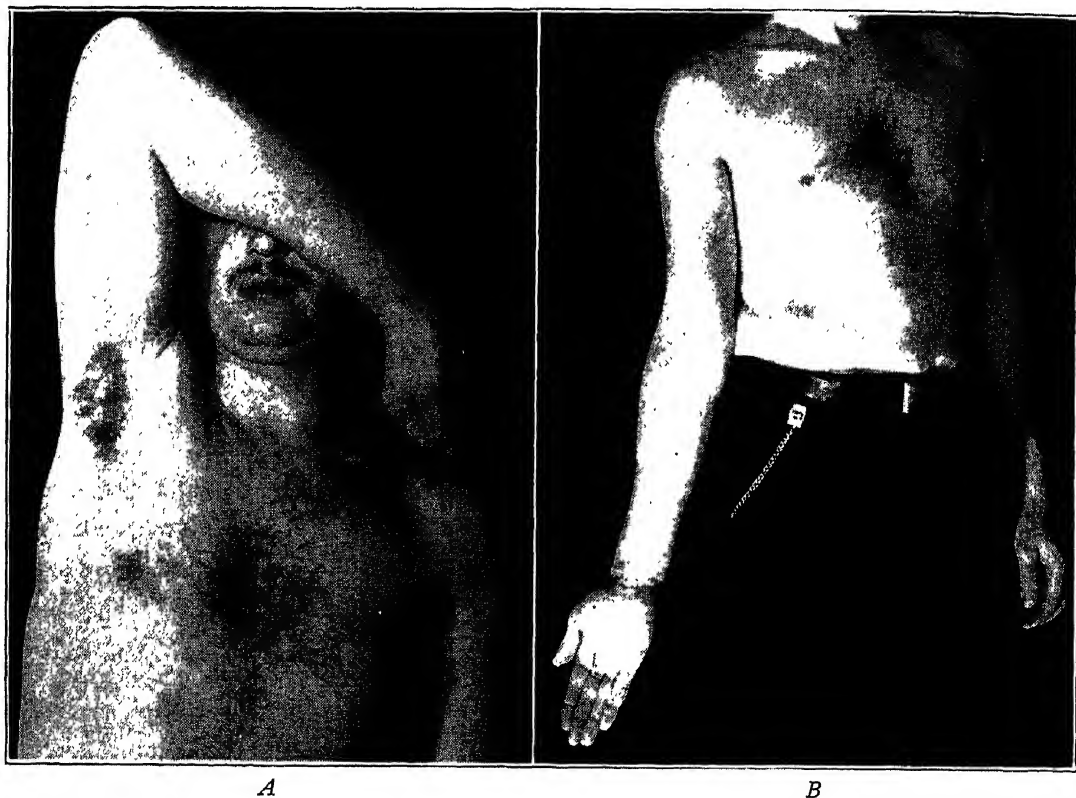


Fig. 57—A, Position of arm producing minimum length of intra-articular tendon. B, Position of arm producing maximum length of intra-articular tendon. (R. K. Lippmann: Arch. Surg.)

and symptoms need not be awaited. Prophylactic treatment of wounds liable to develop gas gangrene should consist of immediate *débridement*, use of *sulfanilamide* in the wound and adequate doses of *tetanus-gas gangrene antitoxin*. X-rays may also be useful as a prophylactic measure. Active treatment should consist of 100 roentgens over involved areas as soon as the diagnosis is made or strongly suspected, repeated twice daily for three days or until the infection is brought under control, local *débridement* and therapeutic amounts of

era of roentgen treatment revealed a mortality of 49.7 per cent. Of the 13 newly reported cases three had a fatal outcome."

### SYNOVIA

**Frozen Shoulder; Periarthritis; Bicipital Tenosynovitis**—"Periarthritis or frozen shoulder is a common disabling illness from which recovery is spontaneous, although its course is protracted and its duration unpredictable." Theoretical considerations have suggested that the basic pathological condition is

a tenosynovitis of the long head of the biceps and its tendon sheath. Surgical exploration in 12 cases showed that this lesion was present in all instances and that no other pathological lesion of the periarticular structures was consistently present. These findings indicate that bicipital tenosynovitis is the pathological

biceps tendon in the bicipital groove. (3) Elevation of the arm in internal rotation causes minimal excursion of the biceps tendon—external rotation, maximum excursion. (4) The greatest excursion of the biceps tendon is produced when the following positions are alternated: (a) The tendon is drawn above into the

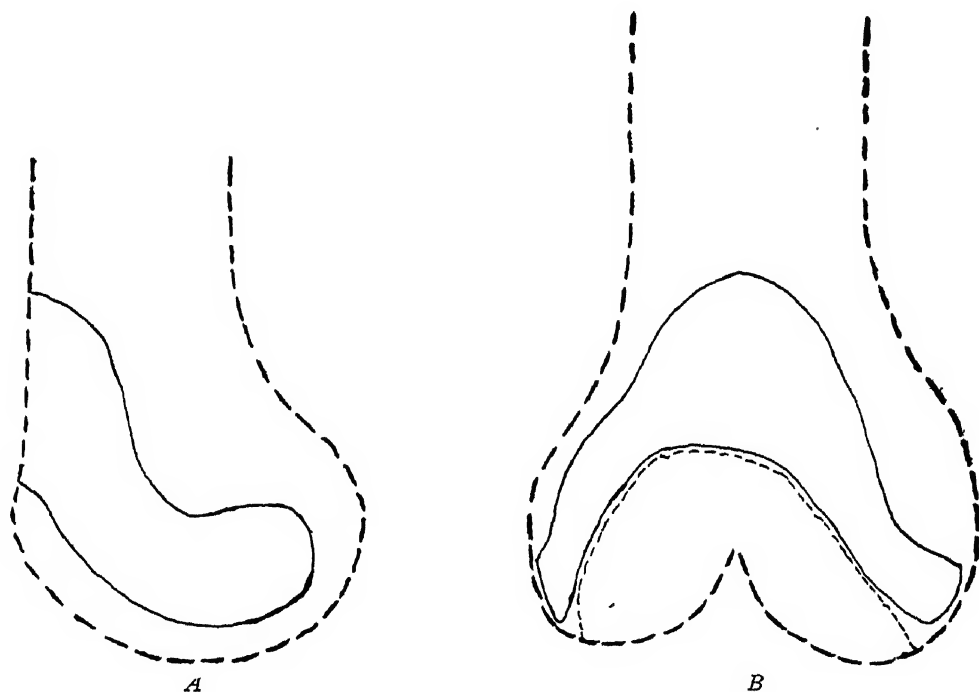


Fig. 58—Size and relative position of the piece of cellophane.  
(D. C. McKeever: J. Bone and Joint Surg.)

basis of periarthrititis in at least the majority of the instances.

The author<sup>30</sup> calls attention to the positions of the arm permitting minimum and maximum length of the interarticular tendon. Four interesting and salient anatomical phenomena were noted following a study of the long head of the biceps tendon in the cadavers on the operating table. They were as follows: (1) No motion of the biceps tendon in the bicipital groove can be produced by contraction or relaxation of the biceps muscle after the shoulder is held immobile in any position. (2) Conversely, any motion of the shoulder joint entails motion of the

groove by elevation, internal rotation and forward flexion; (b) the tendon is drawn into the groove from below by backward flexion and external rotation with the arm depressed.

### Synovectomy

**Hemangioma of the Synovia of the Knee Joint**—Harmon<sup>31</sup> reviews 29 cases previously reported in literature. He calls attention to the fact that many monarticular lesions with recurrent attacks of pain, swelling, stiffness, with bloody fluid on paracentesis, should suggest hemangioma of the synovia. Hemophilia must be ruled out.

**The Use of Cellophane as an Interposition Membrane** — McKeever<sup>32</sup> presents four cases in which No. 300 cellophane was used as a substitute for the synovial membrane following a sy-



Fig. 59—Range of flexion 9 days after operation. (D. C. McKeever: J. Bone and Joint Surg.)

novectomy. In all instances the cellophane was tolerated without evidence of reaction and movement was restored in a remarkably short time. Case 1 had 85 degrees pain-free flexion on the ninth

day. Case 2 had 80 degrees pain-free motion on the fourth day. Case 3—no end result stated. In case 4 a normal range of motion was obtained.

**Comment**—This is entirely too small a series upon which to judge the value of this insulatory substance. However, the swiftness with which movement returns



Fig. 61—Range of flexion finally obtained. (D. C. McKeever: J. Bone and Joint Surg.)

is so striking as to support the author's very modest contentions and more general use of the preparation is indicated.

## MISCELLANEOUS

**Transiliac Amputation** — The authors<sup>33</sup> report six cases of transiliac or interinnomino-abdominal amputation with but one operative death. In each instance the operation was performed for a high femoral or iliac malignancy. Fig. 62 shows the outline of the skin incision. Figs. 63 and 64 show the end result appearances. The authors emphasize the fact that the surgeon must fortify his anatomical knowledge so that he might perform the operation without hesitancy. It is important that the patient receive blood as the operation is carried out.

**Comment**—The details of this operative approach are too minute to incor-



Fig. 60—Range of extension 9 days after operation. (D. C. McKeever: J. Bone and Joint Surg.)

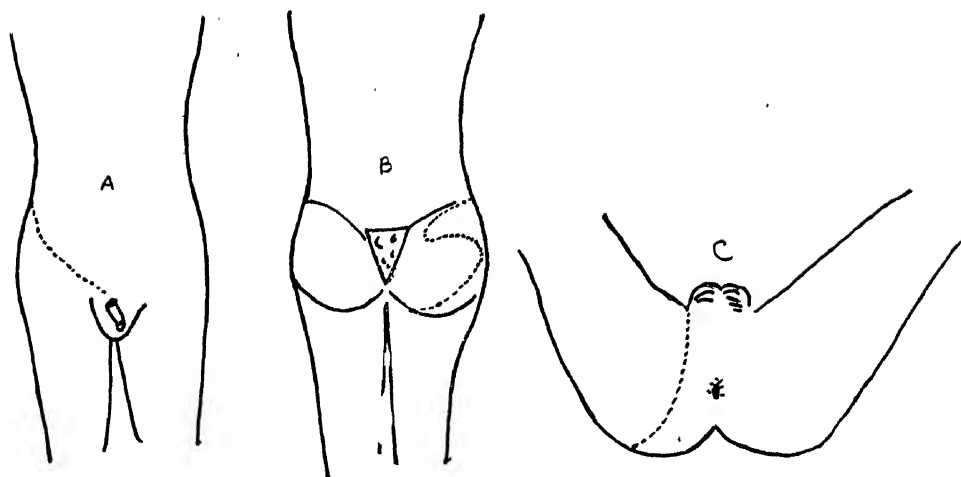


Fig. 62—*A*, Incision for anterior portion of the operation. *B*, Incision for posterior portion of the operation. *C*, Incision for perineal portion of operation. (D. King and J. Steelquist: *J. Bone and Joint Surg.*)

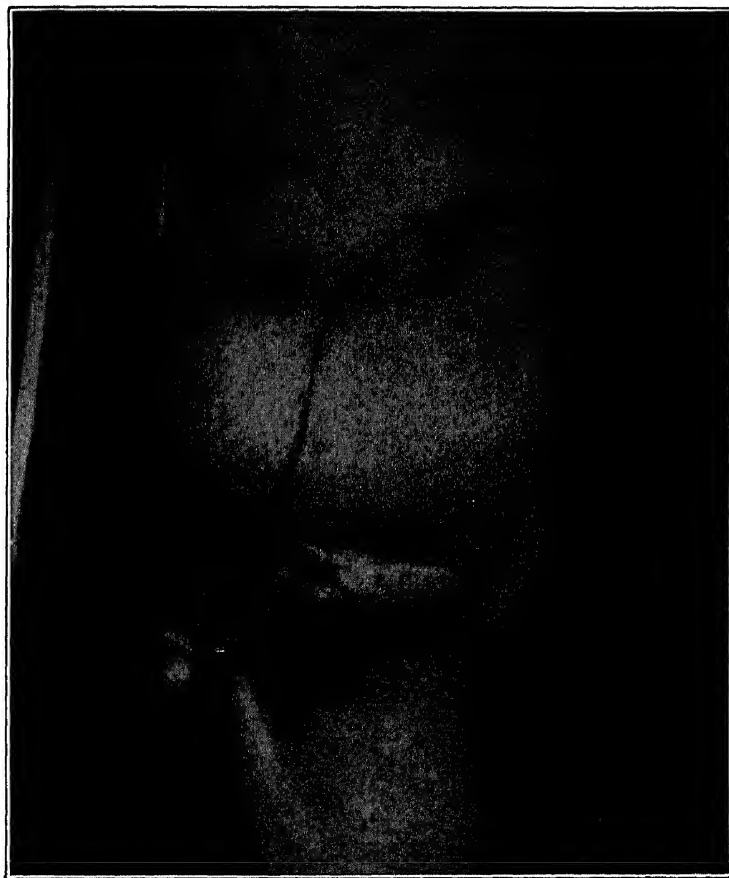


Fig. 63—Showing scar following transiliac amputation. (D. King and J. Steelquist: *J. Bone and Joint Surg.*)



porate in this review. It is suggested that those interested read the original article. The revival of the transiliac or interinnomino-abdominal amputation is well worth while and the splendid operative recoveries noted in the authors' cases indicate its practical nature and

mediately to duty, others were instructed to eliminate weight bearing and protect the ankle by complete rest or on crutches or cane. Twenty-two cases were given *bed rest* for 24 to 48 hours and *hot and cold compresses* were applied; 28 patients were given only *elastic bandage*

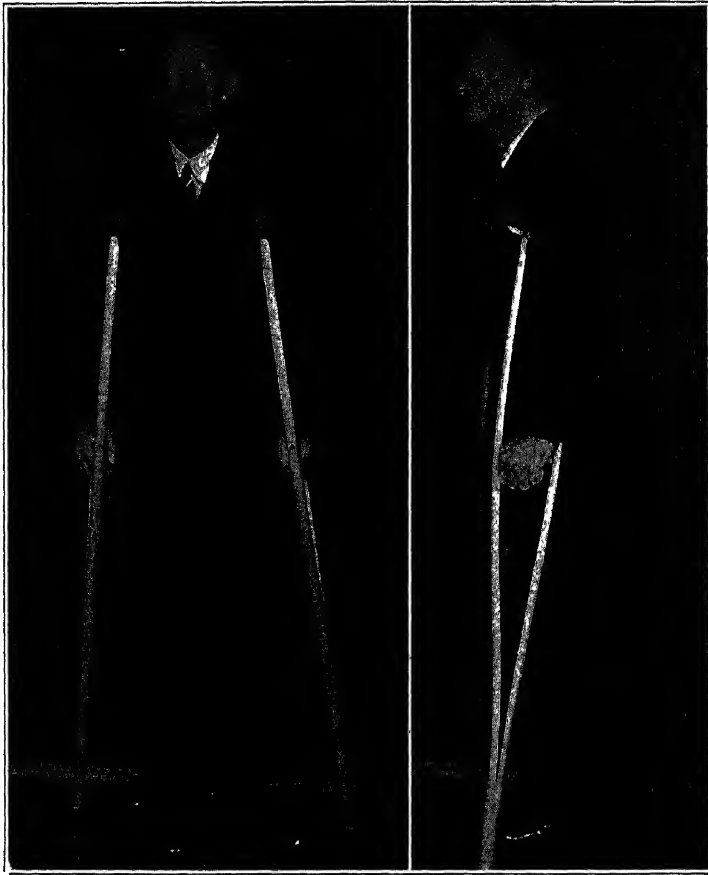


Fig. 64—The patient 3 months later. D. King and J. Steelquist: J. Bone and Joint Surg.)

offer slight but definite hope for some of the high, so-called, inoperable malignancies.

**Treatment of Ankle Sprain** — McMaster<sup>34</sup> reports observations on the various types of treatment employed in 500 cases of ankle sprain. The most common ligament involved is the anterior talofibular, which occurred in over 90 per cent. Various treatments were employed in the 500 cases. Over 200 patients were *strapped with adhesive*, some sent im-

*support*, while 18 with mild to moderately severe sprains were given no treatment. Both groups were sent back to duty immediately. Two hundred patients received injections of *procaine hydrochloride* and with few exceptions were sent to duty immediately. The technic of local injection is that employed by Leriche. Fracture was excluded by x-ray. The sprained ligament was indicated by tender points which were determined by palpation. An antiseptic is applied to the

skin (2 per cent procaine hydrochloride without epinephrine is used routinely) and with it a wheal is made in the skin over the site of the injury with a fine needle. The latter is penetrated by a larger needle and the underlying injured ligament is injected. All tender points, whether proximal or distal, or intervening portions of the ligament, are injected.

ods mentioned above that immediate and continued active motion and use of the sprained ankle and foot, irrespective of any local treatment, definitely hastens recovery. The most satisfactory adjunct in the treatment of ankle sprain in order to maintain motion and use of the foot is the complete elimination of pain by the injection of 2 per cent procaine hydro-

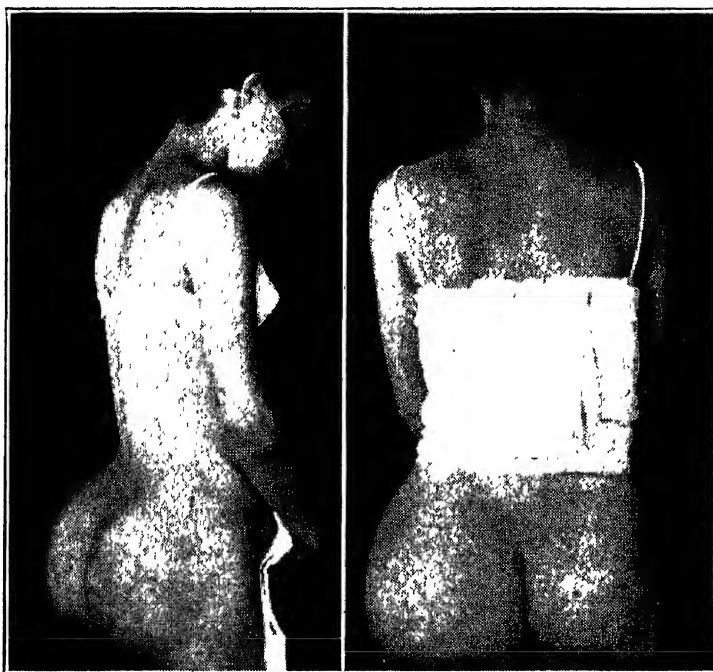


Fig. 65—Appearance of the left gluteal region before operation.  
(A. F. Inclan, Jr., P. Leon, and M. Gomez Camejo: J. A. M. A.)

A search then is made for tender areas in other ligaments and these, if found, are carefully injected.

The amount of the procaine solution varies from 10 to 20 cc. and even an ounce or so has been used in some cases. An elastic bandage is wrapped snugly around the ankle and the patient is asked to walk around the room. If any pain is experienced, further injection is done. The patient is returned to activity with instructions to move and use the foot and ankle normally except for running and jumping.

McMaster concludes after comparing the sprains treated with the various meth-

chloride solution into the injured ligaments.

**Comment**—The reviewer has used procaine injection in a number of cases and has found prompt and favorable relief in young individuals. In older patients, however, it has failed to prove satisfactory.

**Tumeral Calcinosis**—Inclan<sup>35</sup> reports three very interesting cases which he terms tumeral calcinosis. Figs. 65 and 66 are illustrative. These tumors were found in three negro patients, apparently not related. It was characterized by a small steady growth reaching huge size and containing calcareous deposits

imbedded in the connective tissue network. Patients were studied from every possible point of view and all findings were entirely negative, including blood chemistry, Wassermann, study for parasites, etc. An attempt was made to link these cases with calcinosis circumscripta

**Costoclavicular Compression of the Subclavian Artery and Vein**—Three cases<sup>36</sup> of vascular disturbance in the upper limb due to compression of the subclavian artery and vein between the clavicle and the first thoracic rib are described (Fig. 67). In one of these



Fig. 66—Shadow on left illum similar to giant osteochondromatous tumor. (A. F. Inclán, Jr., P. Leon, and M. Gomez Camejo: J. A. M. A.)

and calcinosis universalis and Virchow's metastatic calcinosis, but to no avail. There was no similarity. The microscopic aspect of the calcareous deposits and the chemistry resemble a calcareous granuloma described by Geschickter and Lewis, Adrian, Milian and Neveu.

**Treatment—Resection** and high voltage **x-ray therapy** have arrested, cured, or eliminated the lesion.

**Note**—Ghormley, in a discussion of Inclán's paper, reports a case similar to Inclán's and also calls attention to a case reported in 1898 in the *French Journal of Pathology*, identical with his own. Ghormley believes that these lesions are bursae with an unusual tendency to calcify.

cases in which the cervical rib is demonstrated, the subclavian artery was being compressed at two places—between the scalenus anterior muscle and the apex of the cervical rib, and between the clavicle and the first rib. In a fourth case which showed neurological disturbances only, the subclavian vessels were not compressed and relief was obtained by a section of fibrous band compressing C 8 and T 1 nerve roots without division of the scalenus anterior.

Costal clavicular compression of the subclavian vessels can be recognized by observing the effect of postural maneuvers of the shoulder girdle on the arterial pulses of that limb. Backward and downward placing of the shoulders is the

movement which obliterates the pulses most readily. The subclavian vessels can be compressed by these maneuvers in any normal subjects. Symptoms arise only when this compression is easily provoked and, if compression is not relieved at an early stage, features of obliterative arterial disease may supervene. Symp-

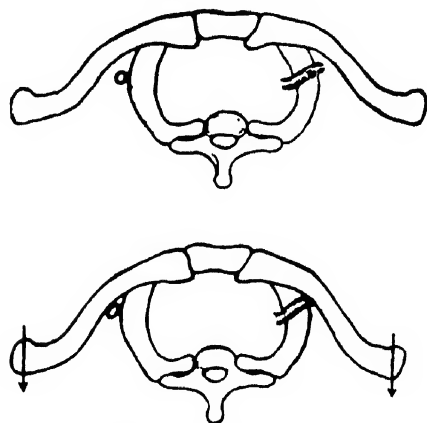


Fig. 67—Diagram illustrating mechanism of costoclavicular compression of subclavian artery on backward and downward bracing of shoulders. (M. A. Falconer and G. Wedell: Lancet.)

toms range from cold, blue hands with a tendency to chilblains in the mildest group of cases to "Raynaud's attacks," arterial thromboses, and even gangrene in the more severe cases.

In the mild cases, benefit may be obtained by **remedial exercises** designed to increase the postural tone in the muscles of the shoulder girdle. In more severe cases, an operation is required and this is best done under local anesthesia. The site of compression of the subclavian artery between the clavicle and the first rib is demonstrated by getting the patient to place the shoulders backwards and downwards. In positive cases, the tip of the forefinger is nipped between the clavicle and rib, and the radial pulse disappears. The essential part of the operation is the **removal of the segment of the offending rib from be-**

**neath the artery.** The division of the scalenus anticus muscle alone may be ineffective.

**Bloodless Reduction of Congenital Dislocation of the Hip**—Gill<sup>87</sup> presents the end results of a bloodless reduction of congenital dislocation of the hip. The total number of cases was 253, females 204, 80.5 per cent.; males 49, 19.5 per cent. The total number of hips involved were 322, bilateral 69, or 27.5 per cent, and unilateral 184, 72.5 per cent. Of the unilateral, the right hip was 42 per cent, and the left 58 per cent. The number of bloodless reductions performed by the author was 180. Open operations numbered 162.

The conclusions of the author are as follows:

"1. The condition of predislocation of the hip can be recognized. The appropriate treatment can prevent subsequent dislocation, although the author does not know whether it will always prevent it.

"2. A dislocated hip should be **reduced bloodlessly**, if possible, as soon as the dislocation is recognized—the earlier the better.

"3. If bloodless reduction is impossible, **open reduction** should be done.

"4. Careful and systematic observation of all hips reduced by manipulation or by operation should be maintained at least until the age of puberty has been passed, unless perfect structural development has been attained in the meantime.

"5. Redislocation and subluxation should be recognized early, and should be treated by an **operative procedure** that should reconstruct an acetabulum as near to a normal acetabulum as is possible.

"6. Dysplasia of the acetabular roof, whether of short or of long duration, does not demand operation unless it is

accompanied by persistent or increasing subluxation.

"7. The onset of symptoms during any of the years subsequent to reduction indicates imperfection in the anatomical structure of the hip, and calls for a *reconstructive operation*.

summary. One thoroughly acquainted with these principles may regard himself well versed in the congenital hip problem.

**Posterior Hernia of the Knee**—The authors<sup>38</sup> present 15 cases in which popliteal cysts produced firm, fixed masses

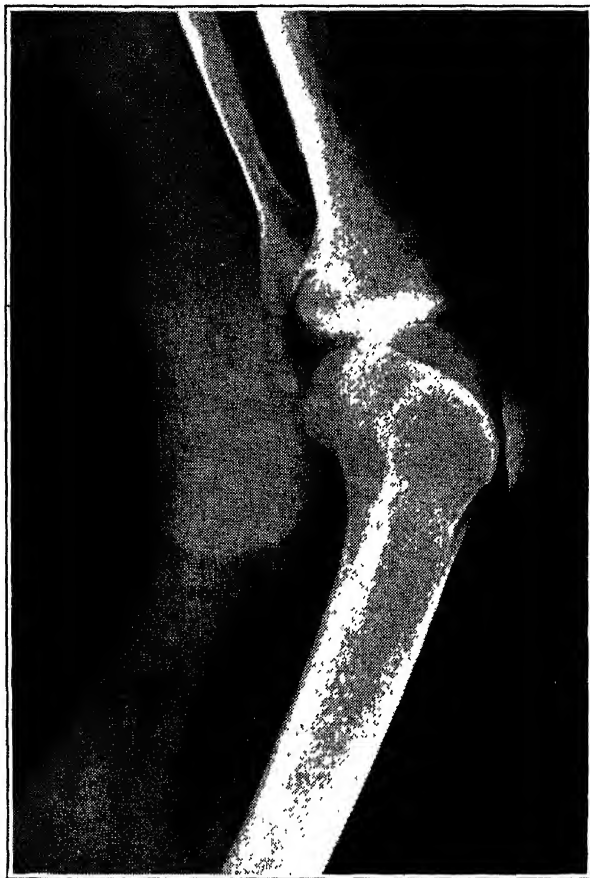


Fig. 68—Large cystic mass at knee which at the time of operation was found to contain fluid and was connected directly with the joint (lateral view). (H. W. Meyerding and R. E. VanDemark : J. A. M. A.)

"8. Until perfect anatomical structure and relation have been attained, the congenital dislocation cannot be considered 'cured,' no matter how perfect the function."

**Comment**—The article is beautifully illustrated and the conclusions of the author are well supported by statistics and illustrations. One must read the entire article to appreciate the solid fundamental principles involved. The reviewer is particularly impressed with the

and in some instances limitation of flexion of the knee and swelling in the popliteal space. Each of these cysts at the time of surgical intervention were found to be connected directly with the knee joint through an opening in the posterior part of the capsule, usually along the lateral side of the medial condyle of the femur.

The writers were of the opinion that a herniation of the synovial membrane through the posterior capsule or the es-

cape of fluid through the normal anatomic connections of the knee into the bursae (medial gastrocnemius or the semimembranosus) were responsible for the cyst. The literature is carefully reviewed. Baker published the first article on synovial cysts of the knee in 1877. Adams, Gruber, Cravener, Haggard, and Wilson add to our knowledge con-

Legg-Perthes disease by Gill<sup>39</sup> presents no evidence that this condition is due to hypothyroidism.

**Note**—Cavanaugh, Shelton, and Sutherland in 1936 called attention to the possible relationship of metabolic (thyroid deficiency) disturbances and Legg-Perthes disease. The history of goiter in parents, retarded development of bones

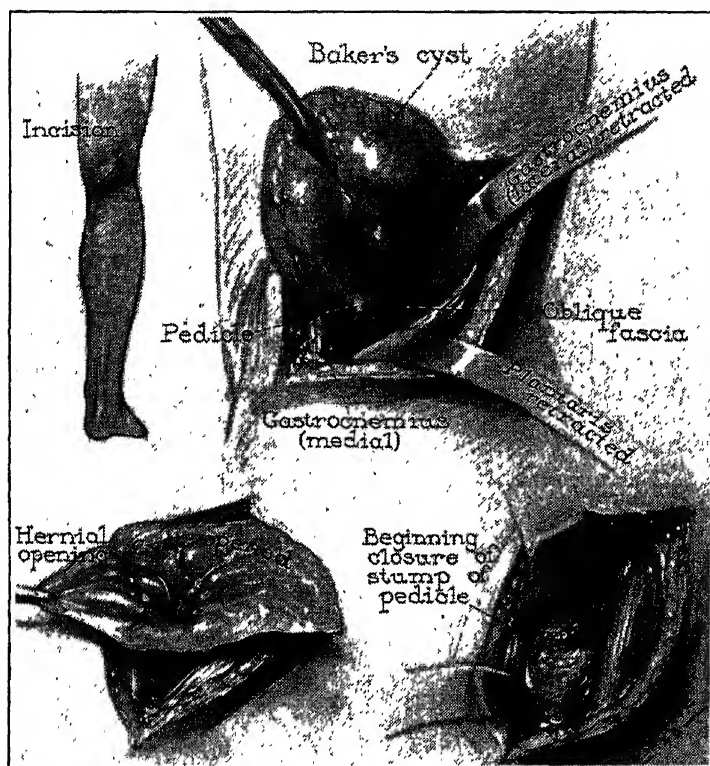


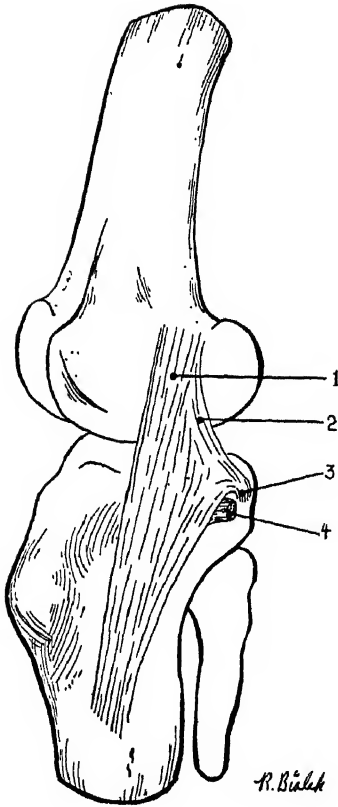
Fig. 69—The surgical technic employed: The oblique incision over popliteal space and along the course of the cyst; the cyst dissected free and pedicle exposed at the point of entrance into the joint; cyst opened to show inner surface and hernial opening into the joint and pedicle exposed after excision of cyst. (H. W. Meyerding and R. E. VanDemark: J. A. M. A.)

cerning them. The authors recommend surgical removal and point out the very important fact that in no cases have there been any recurrences, provided the capsular defect produced by the excision of the cyst is closed. Wide excision of the pedicle leaving the capsule open predisposes to recurrence. Figs. 68 and 69 are illustrative.

**Relationship of Legg-Perthes Disease to the Function of the Thyroid Gland**—A careful study of 20 cases of

and faulty dentition, hypogenitalism, cryptorchidism, enuresis, palpable thyroid gland, and dryness of skin and hair were studied. The author carefully studied the case reports of Cavanaugh, Shelton, and Sutherland and feels that the nonweight bearing treatment by the above was probably more important than the endocrine therapy.

**The Tibial Collateral Ligament**—Brantigan and Voshell<sup>40</sup> bring to our attention the anatomy of the tibial col-



lateral ligament, which is composed primarily of parallel and oblique portions with emphasis placed upon the fact that the parallel fibers normally thought to be connected with the internal meniscus are in no way associated with this structure. Two bursae lie beneath the parallel fibers, one at the upper end of the ligament between the parallel fibers and the femur and a lower one located between the parallel fibers and the tibia. Calcification of the upper of these two bursae is offered as a possible explanation

Fig. 70—A stripped joint showing a diagrammatic view of the tibial collateral ligament. 1, Parallel portion of the tibial collateral ligament. 2, Oblique portion of the tibial collateral ligament. 3, Attachment of the oblique portion of the ligament posterior on the tibia, just inferior to the tibial articular surface and lateral to the insertion of the semimembranosus tendon to the tibia. 4, Insertion of semimembranosus tendon to the tibia. (O. C. Brantigan and A. F. Voshell: J. Bone and Joint Surg.)

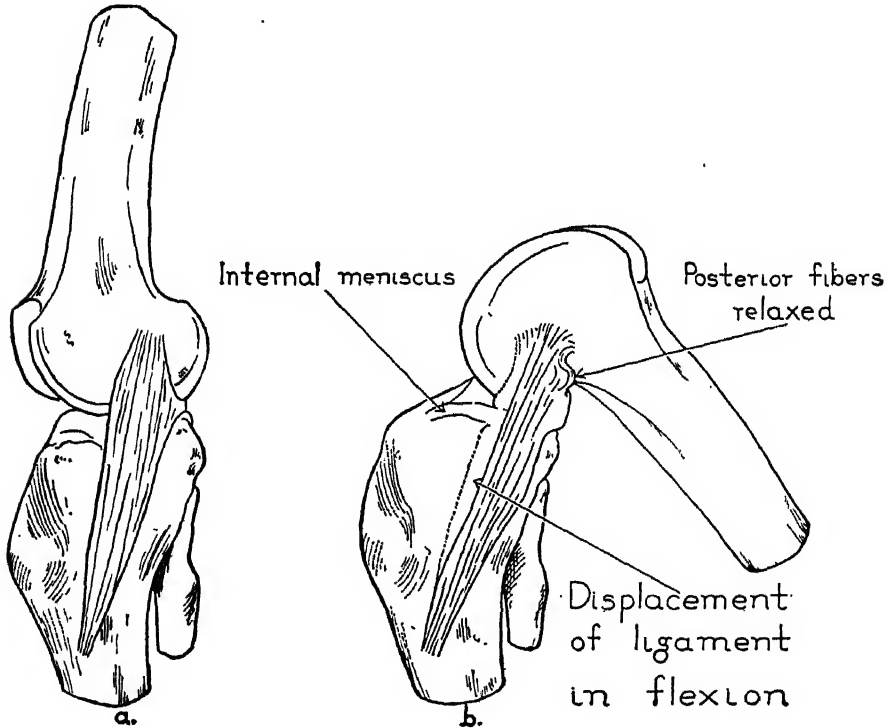


Fig. 71—A stripped joint showing the tibial collateral ligament. a, In extension, tension on the tibial collateral ligament is distributed throughout its width. b, In flexion, the area of tension is shifted to the anterior parallel portion of its fibers, while the posterior oblique portion is relaxed. Some portion of the ligament is taut in every position. The sliding of the ligament backward in flexion and forward in extension is indicated. (O. C. Brantigan and A. F. Voshell: J. Bone and Joint Surg.)



tion for some of the cases of Pellegrini-Stieda disease. The bursae vary in number and size and may be as high as five in number but located at different levels of the collateral ligament, and between

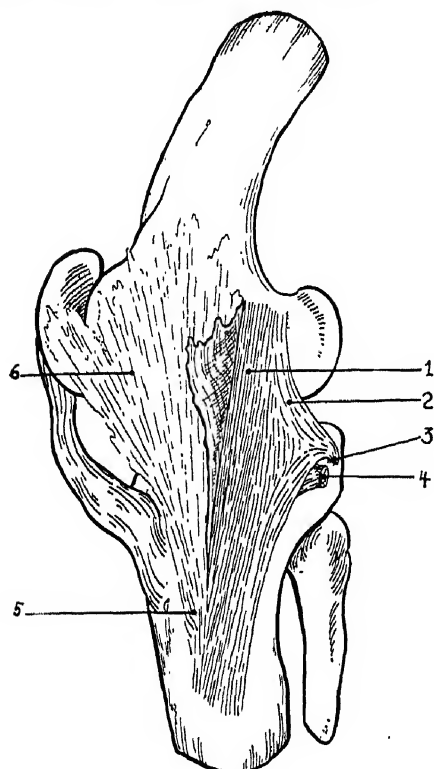


Fig. 72—A medial view of a knee joint, showing a fibrous fanlike membrane which is indistinguishable from the tibial collateral ligament at its anterior attachment to the tibia. 1, Parallel portion of the tibial collateral ligament. 2, Oblique portion of the tibial collateral ligament. 3, Attachment of the oblique portion of the ligament posterior on the tibia, just inferior to the tibial articular surface and lateral to the insertion of the semimembranosus tendon to the tibia. 4, Insertion of the semimembranosus tendon to the tibia. 5, The area on the tibia where the fibrous fanlike membrane is indistinguishable from the attachment of the tibial collateral ligament to the tibia. 6, Indicates the extent of the fibrous fanlike membrane and shows it reflected from the superficial surface of the tibial collateral ligament. (O. C. Brantigan and A. F. Voshell: J. Bone and Joint Surg.)

this ligament and the underlying structures. Figs. 70, 71, 72, and 73 clearly demonstrate the ligament and its relationship to flexion and extension and its relationship to the two most important bursae.

**Comment**—This presentation adds to our knowledge of the tibial collateral ligament and points out a possible explanation for the pathology in Pellegrini-Stieda disease.

**Intractable Pain About the Fourth Metatarsophalangeal Joint (Morton's Toe)**—McElvenney<sup>41</sup> reviews the subject of Morton's toe and makes a contribution to this perplexing problem which points well towards the solution of the entire difficulty. Figs. 74 and 75 clearly point out the conception of the pathology underlying the condition. He shows it to be a painful affliction of the foot caused by a tumor involving the

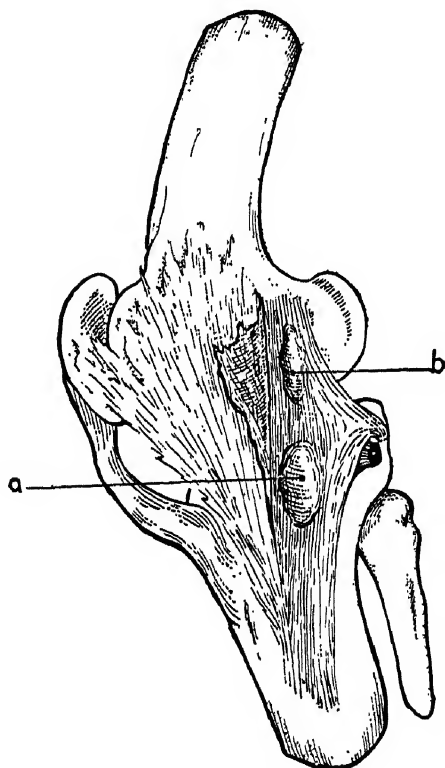


Fig. 73—Medial view as in Fig. 72, showing section of the ligament removed over the bursae (a and b). (O. C. Brantigan and A. C. Voshell: J. Bone and Joint Surg.)

most lateral branch of the medial plantar nerve. Careful palpation will usually reveal the tumor, which lies high in the web between the third and fourth toes. Treatment consists of *excising the tu-*

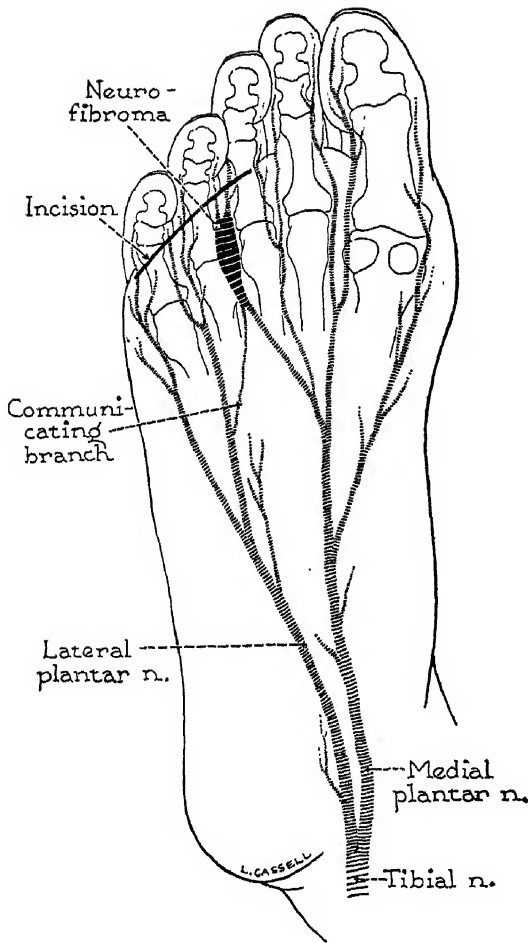


Fig. 74—Showing the anatomy of the parts. The incision shown is the first one used. Note that the location of the tumor is farther forward than the metatarsal heads. (R. T. McElvenney: J. Bone and Joint Surg.)

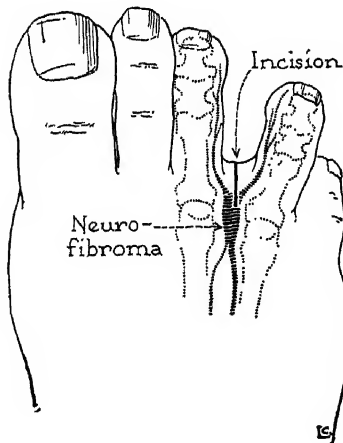


Fig. 75—Showing the location of the tumor and the type of incision that is preferred. The incision should extend more proximally than is shown. (R. T. McElvenney: J. Bone and Joint Surg.)

*mor* if symptoms justify it. Twelve such tumors have been removed in 11 patients; five of them had microscopic studies and the pathology appeared to be either a neurofibroma or angioneurofibroma (Fig. 76).

**The Sacroiliac Joint and Pain of Sciatic Radiation**—The author<sup>42</sup> has made a very careful anatomical study of the anterior sacroiliac lesions of 64 embalmed bodies. He concludes that "the lumbosacral trunk was in direct contact with the sacroiliac joint at the point at which it traverses the joint in its lower one-third in all of the 64 specimens studied. The upper portion of the origin of



Fig. 76—On the left is a normal fourth digital nerve taken from a fresh specimen. On the right is a tumor of the fourth digital nerve. (R. T. McElvenney: J. Bone and Joint Surg.)

the piriformis muscle was found to lie medial to the lumbosacral trunk in this study and never to lie between the trunk and the joint. Hypertrophic arthritis in the form of severe spur formation in the anterior line of the sacroiliac joint was found to be present in 25 per cent of the bodies that were studied. Most of these were considered capable of producing direct irritation of the lumbosacral trunk."

**Comment**—The author reviews the literature on the subject and points out that John Hilton in his lectures to the

Royal College of Surgeons was the first to demonstrate the close anatomic relationship between the lumbosacral trunk and the sacroiliac joint. Golthwait, Osgood, Albee, Danforth, Wilson, Yoeman, Sashin, Willis, and others further confirmed Hilton's observations. It is hard to evaluate the importance of the paper in view of the fact that the author made no comment on the histories of the cases in which he found the marked arthritic changes in the sacroiliac joints. Perhaps these were not available. That sacroiliac arthritis may possibly involve the lumbosacral trunk is worth while thinking of, but until the clinical data are supplied to confirm this definitely, the practical application of this paper will be restricted.

**Some Surgical Lessons of the War<sup>43</sup>—Gunshot Wounds—Sulfonamide therapy** is the outstanding new feature of wound treatment in this war. Its value by oral administration has been proven. Excision of the bruised skin and excision of the damaged muscle, spreading of the deep fascia to insure drainage, dusting of sulfonamide powder over the exposed surfaces, covering with vaseline gauze, are the factors involved in immediate or early treatment. Sulfonamide in too great a concentration will produce peripheral nerve damage. It should always be insufflated or dusted in the wound and not poured in bulk. Two cases of severe peripheral nerve injury were attributed to too great a concentration of sulfonamide. The wound should not be sutured in the forward area. This is the old teaching and still holds true. A skin-tight plaster with padding over the bony points is the choice of immobilization. The valuable pioneer work of Orr in the last war and of Truetta in the recent Spanish Civil War is responsible for this method now universally adopted.

**Tobruk Plaster**—The Tobruk plaster is employed for the treatment of a fractured femur. The wound toilet is completed, a transverse division of the deep fascia is made to insure deep drainage, a large soft dressing is applied to the wound area, skin traction by elastoplast is added with ample protection for the malleoli, weight and pulley are attached temporarily to keep up moderate traction, the knee is kept moderately flexed, and a skin-tight plaster is applied from groin to toes with the foot at right angle. Two large holes are cut out around the malleoli to allow the elastoplast traction a free exit. As soon as the plaster is set, a Thomas knee splint with a big ring is put on and then the elastoplast traction is applied to the end in the usual way. The ring is made to fit by putting padding between it and the plaster on the outer side. The plaster is then split from top to bottom. No skin-tight plaster should ever be applied to a patient who is going to be evacuated and transported to a base hospital unless the plaster has been split. Disasters have occurred and will occur unless this is done.

**Plaster Spica**—Its use is restricted largely to the base hospitals. It is too bulky to be employed in transit, a Jones abduction frame being by far the most satisfactory splint for transportation. It is particularly useful in fractures of the pelvis, hip, and lumbar spine. The shoulder spica as a splint during transportation is condemned by practically all surgeons. A collar and cuff sling, reinforced by an arm and forearm plaster splint, has become the standard transportation splint.

**Amputations** — Experience shows that amputations done in the forward areas when the patient is to be evacuated must never be closed. The flap must not be sutured even if drainage at the sides is to be employed. Amputations should

be performed as low down in the limb as possible, cutting skin flaps and sewing them back but never closing them. Then *petroleum jelly gauze dressing* is applied.

The same old mistakes which we learned to avoid during World War I have again given the most trouble. We must remind ourselves that wounds must be left open and not sutured and that amputation flaps must not be closed. The plugging of wounds must be avoided. Vaseline gauze should be used as a covering and not as a plug and that skin must not be sacrificed unnecessarily in performing wound toilet. We must remember to put the foot at right angle and not in equinus and that fractures require traction as well as fixation to get the necessary rest and that fixation must be as nearly as possible absolute.

**Peripheral Nerve Injury**—There is only one way to repair a nerve defect and that is to carry out end-to-end suturing. Cable grafts have proven successful in animals but not successful in human beings.

**Injuries in Training**—*Internal Derangement of the Knee*—No operation should be performed unless the surgeon is certain of the diagnosis and has tried out the joint with provocative physiotherapy. No operation should be performed in the presence of laxity of the crucial ligaments or a mild degree of arthritis.

**Foot Strain**—In general avoid operations on soldiers' feet with the exception of straightening a single hammer toe. An operation on a hallux, so successful in peacetime, is seldom successful in retaining a man in high category. The principal fault here has largely been due to the failure to appreciate the need for a preliminary rest period. Fractures of the os calcis are more common than in

peacetime. They are produced by land mines, by bombs between decks, and many other ways. Many of these fractures are hopelessly comminuted. They generally become painlessly ankylosed but if not the joint is arthrodesed.

*Fractures of the carpal scaphoid* have had satisfactory results if diagnosed early, reduced, held fixed and protected until consolidated. Late fractures have disappointing results. Grafting seldom returns a man to his Army category. He cannot handle a rifle.

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## PLASTIC AND RECONSTRUCTIVE SURGERY

HANS MAY, M.D., F.A.C.S.

### BURNS

**Skin Grafting of Burns** — Brown and McDowell<sup>1</sup> write concerning the repair of deep burns with free skin grafts. In addition to the main topic, they discuss primary care and treatment. The chapter on primary case discusses control of shock and toxemia, and early local care of the burned area. As the local treatment of burns, the authors prefer the *open surgical drainage* consisting of thorough cleansing under aseptic precautions, débridement, and dressings with either wet saline or ointment. They also discuss the closed or "sealing" methods such as the *tannic acid treatment*, etc.

The chapter on spontaneous healing of burns makes an excellent introduction to the main topic of the book. In deep burns, healing must necessarily occur by granulation tissue, which becomes covered with scar epithelium derived from the surrounding skin. This scar epithelium, however, lacks the derma that is really important in giving bearing protection. Occasionally, a patient may heal a wide full thickness loss and may even get permanent bearing function. Others may heal rapidly, but usually with so

much dense, deep fibrous scar tissue that marked deformities are produced. Other patients apparently do not grow any epithelium, and can linger on over long periods.

Hence, the local care of the burned area can be summarized under the dictum: "Get the areas as clean as possible and restore what full thickness skin has been lost with free skin grafts."

The main topic of the book, consisting of early skin grafting of the raw areas and the repair of late contractures and deformities, has been described in an exhaustive and authoritative manner.

The remarkable results as demonstrated by copious illustrations are the fruits of many years' observation and experience.

**Push-back Operation** — Dorrance and Bransfield<sup>2</sup> improve the push-back operation by two additional procedures. The first of these is the use of the mucoperiosteum of the vomer, after Lannelongue and Veau, to form a flap which is sutured under the palatal mucoperiosteum, thus closing off the nose from the oral cavity. The second addition is the lining of the palatal mucoperiosteum flap with a Thiersch or split-skin graft. The

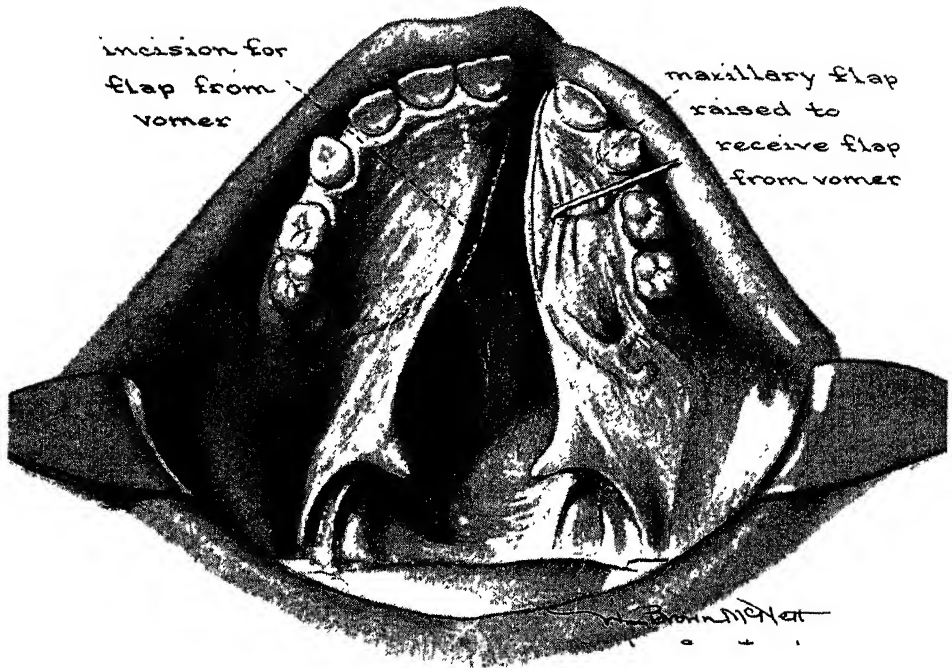


Fig. 1—Incision for the vomer flap. (G. M. Dorrance and J. W. Bransfield: Ann. Surg.)

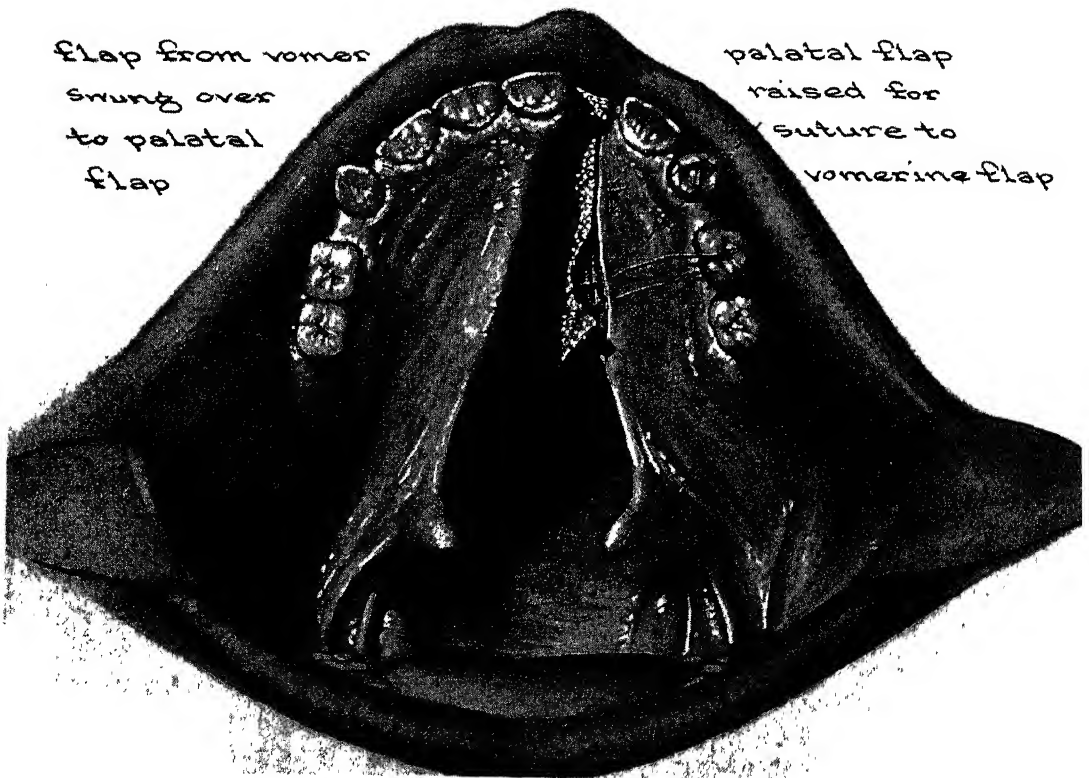


Fig. 2—Suturing of the flap in the vomer transplantation.  
(G. M. Dorrance and J. W. Bransfield: Ann. Surg.)

graft is sutured in place under each flap, raw surface to raw surface. Since adopting this procedure, crust formation has been diminished and contracture of flaps when finally displaced backward in the second stage is either completely eliminated or greatly minimized. In order to

subdivided into two or more portions, one of which was covered by a standard and the others by experimental preparations. Healing was judged to have taken place when the wound became closed, that is, when the surface was covered with intact epithelium, unbreakable

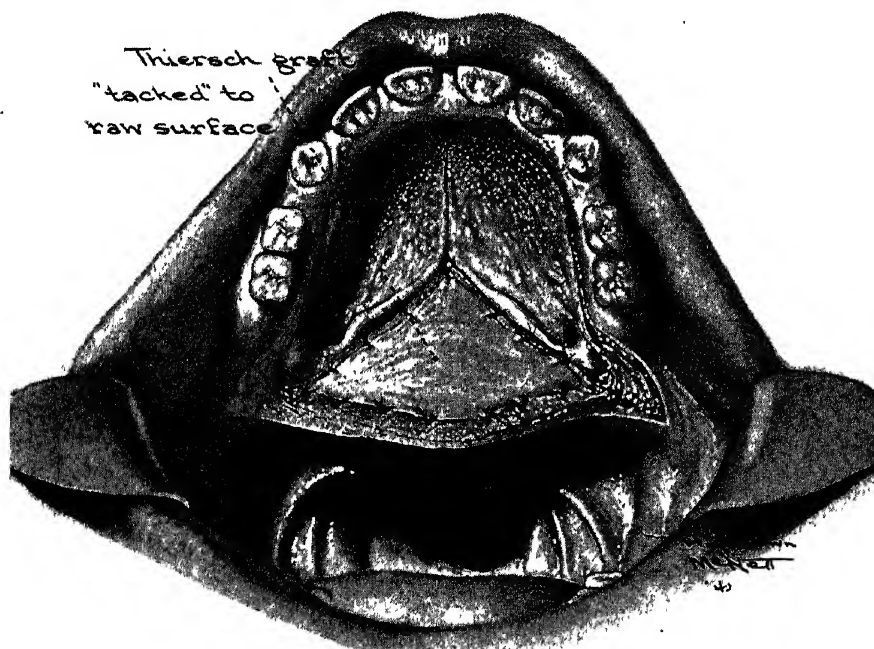


Fig. 3—Flap elevated. Skin graft sutured in place. (G. M. Dorrance and J. W. Bransfield: Ann. Surg.)

assure a take, pressure on the flap is necessary. This is accomplished by placing iodoform gauze over the flaps. The gauze is maintained at a constant fixed pressure by wire fixation or by a special splint designed by Dr. T. Gross.

**Boric Acid Treatment**—Cannon and Cope<sup>3</sup> are among those who have felt that the tanning methods in vogue for the treatment of burns are injurious to the viable epithelium of the burned patient. To study and measure the effect of various substances upon the rate of epithelial regeneration in humans, they used the donor area from which a graft of uniform thickness is cut. The dermatome was used and a standard depth of 0.012 inch was chosen. The donor area was

by the trauma of ordinary activity. The reparative process continued beyond this point, but this stage of healing was chosen because it could be ascertained clinically. It was the stage at which a dressing could first be removed without causing bleeding. Various agents recommended for the treatment of a débrided burn surface were tested by applying them to the donor areas. *Tannic acid*, *tannic acid and silver nitrate*, *gentian violet*, the *triple dyes*, and *triethanolamine* solutions, all were found to delay epithelial healing as compared with the control *boric acid* treatment.

Hirschfield<sup>4</sup> conducted experiments similar to Cannon's and Cope's, and came to the same conclusion that the



donor sites of skin grafts healed more quickly with less discomfort when treated with *vaseline gauze* than when treated with tannic acid. Tanning agents produce an extensive tissue damage of the derma, to form the eschar, while vaseline gauze produced a minimum damage.

Cope<sup>5</sup> describes a simple treatment for the surface wounds of burn casualties. This treatment was given extensive trial on the surface burns of the casualties from the Cocoanut Grove fire treated at the Massachusetts General Hospital. It consisted of application of a *bland ointment* without any preliminary débridement or cleansing, followed by a *protective pressure dressing* and *internal antibacterial chemotherapy*.

Cope comments that the use of this unorthodox surface treatment was premeditated and prompted by the concept that of treatments giving approximately equal results, the simplest would be the one best adapted for a disaster with numerous burn casualties. The result of this treatment has been considered by the hospital staff as gratifying. The problem of débridement and cleansing cannot be categorically answered for all burns. If a burn surface has been rubbed in dirt, more infection may be avoided by débriding and cleansing. Good surgical judgment, as in many other diseases, consists of knowing when not to interfere.

Cannon<sup>6</sup> describes procedures in rehabilitation of the severely burned cases of the casualties from the Cocoanut Grove fire treated at the Massachusetts General Hospital. The primary occlusive dressing of a fine mesh gauze lightly impregnated with boric acid ointment and applied with firm pressure has already been described by Cope (see previous paragraphs). Similar dressings were used after the first were changed between

the fifth and tenth days. By the tenth to twelfth day, the destroyed skin had begun to separate and there was sup-puration about the margins with pus escaping through openings in the slough. No cellulitis or lymphangitis indicative of invasive infection was apparent. In order to insure better drainage of the wounds, constant wet dressings, with a single layer of fine mesh gauze against the granulations were applied at this time. The Bunyan envelope was used for several days in four patients who had burns of the hands and forearms. The patients found them uncomfortable. The average time before complete separation of the slough was 25 days. The maximum was 36 days, and the minimum 16 days. An effort was made to hold the hands in the position of function, but this could not be continued because of the pain. Therefore, the fingers were allowed to remain in extension and the wrist in a neutral or slightly dorsiflexed position. This position was maintained until operation, at which time the hand and fingers were splinted in a more nearly normal functional position.

**Preparation for Grafting**—The use of wet dressings applied with moderate pressure was continued after the slough had separated. The wet dressings acted as a keratinizing stimulus, particularly on the areas of second degree burn adjacent to the granulations and on the advancing marginal epithelial surfaces. This débris did not develop when an ointment dressing was applied. The débris, which became macerated, grew staphylococci and saprophytes on culture. At each change of dressing the surfaces were carefully cleaned with soap and water to reduce as much as possible this source of contamination of the wounds. The persistence of infection and edema of the granulations after the slough had

separated may be attributed in part to this maceration. In most of the cases general *chemotherapy* had been discontinued before the time of grafting. All patients were given a *high protein* and *high vitamin diet* throughout the hospital stay. Anemia was controlled by repeated *whole blood transfusions*.

**Operative Procedures**—Split-thickness grafts were used for covering the raw surfaces with the exception of the back of the hand in one case, which was covered by a direct abdominal flap. At operation, the raw surfaces were prepared with soap and water. The granulations and the narrow zone of skin that had grown in about the margin were shaved off in almost all cases. All post-operative dressings were applied wet and kept wet by irrigation through Dakin's tubes. A single layer of fine mesh gauze was used against the graft, and the overlying dressing consisted of sponges and a thick layer of mechanic's waste held firmly in place with cotton bandages. Sterile, well-padded wood splints were used to immobilize the hands and arms after operation. A bulky dressing was sufficient for fixing the ankles and feet, but padded wood splints were used at the knees. The first dressing was done on the fifth or sixth day after operation. *Boric acid ointment gauze* was applied in all cases. Subsequent dressings were done on alternate days as long as was necessary.

**Wounds**—Sheehan,<sup>7</sup> in three consecutive articles, discusses war wounds, burns as war wounds, and tissue grafting. Each article represents a symposium of the clinic and the present-day treatment of the subject discussed and can be considered as an excellent reference. (SEE: *War Surgery*, p. 927.)

## FLAPS AND GRAFTS

**Rhinoplasty**—Gillies,<sup>8</sup> on looking for an improvement in the method of making a nostril, was intrigued by the fact that the normal nostril is lined by a very thin piece of skin closely adherent to a thin piece of cartilage. Such a piece of skin and cartilage is readily available in the concha of the normal ear. The skin on the front of the concha is very closely adherent to the thin cartilage, and the curve of the cartilage is similar to that required in making a nostril. In order to prove that such a piece of cartilage and skin grafted under the covering flap would make a good nostril, three rhinoplasties were done in which the covering flap was made to approach the ear in such a way as to pick up this combination of cartilage and skin as a living flap. When the cartilage and skin has adhered to the living flap it could then be safely divided from its remaining attachment to the ear and left adhering to the covering flap. Having proved its general value, it remained to make the apparently risky procedure of cutting out a portion of the skin and cartilage of the concha in one piece and making a free graft of this under that part of the forehead destined to make the new nostril. The free chondrocutaneous graft succeeded *in toto* and the new nostril margin, when the nose was made, has proved to be delicate in shape and voluminous as regards its opening. In making such a free graft, a larger piece of skin was cut than of cartilage, and it is a moot point whether the blood supply into the graft came through this fringe of skin to the middle of the patch of skin, or whether some blood supply or nourishment penetrated the cartilage, and so reached the adherent skin on its concave surface. That such a combined graft will survive is an interesting fact, and one which may lead to its use in other

regions in which the thin epithelium backed by suitable cartilage support is required; for instance, it should make the basis of a very excellent eyelid, when the globe is not present and one of the lids has been destroyed. It might also be used in stenosis of the larynx and trachea, and in collapsed alae nasi.

**Limb Wounds**—Brown,<sup>9</sup> in discussing repair of limb wounds by the use of direct skin flaps offers an improvement of the plaster cast fixation in the case of cross-leg flaps. On the day prior to operation, after the last preoperative plan has been made, the patient is placed in the position which he will occupy after operation. Three separate sections of plaster are then applied; for example, round both thighs and one leg. The legs should be washed thoroughly with soap and water beforehand, but not shaved, so that the nonpadded casts will adhere to skin and hairs. Change of posture is avoided as far as possible during drying of the plaster.

At operation 24 hours later, the plaster is dry and firm. All that is necessary after the operation is completed is that the three sections be joined by a triangle of stout plaster rope, while the limbs are held in the required position by an assistant. This can be done in a few minutes, and with minimal contamination of the wound. The slight contamination that does occur is not of great importance. It is far more important that the flap should be exposed till the fixation is completed. Only then can the surgeon be quite certain that the posture is right. After a few minutes to allow the plaster rope to harden, the patient can be bundled into bed with scant ceremony, the two legs moving together. The plaster design will vary with the type of case; the principle of application remains the same.

**Cheek Defects**—MacFee<sup>10</sup> describes and illustrates a method of repair for full thickness defects of the cheek involving the angle of the mouth. It consists in sliding a large bridge flap of skin and anterior mucous membrane lining from the neighboring parts of the cheek.

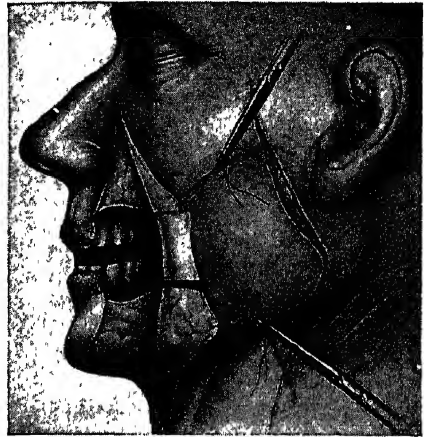


Fig. 4—The anterior margin of the flap has been raised in a manner similar to the elevation of the posterior margin. The buccal mucosa is included as a part of the flap. The dotted line indicates the position of the incision made in the underlying mucosa from the posterior approach. (MacFee, W. F.: Surg., Gynec., and Obst.)

**Skull Depressions**—Peer, in repairing defects of the skull and other depressions, uses cartilage grafts cut into many fine squares. These fine cartilage squares are introduced into an exposed depression of the skull, for instance, and gently patted into a rounded contour, and the skin of the scalp sutured over the rounded surface of the cartilage mass. This method has an advantage over the use of segments of cartilage grafts—the larger grafts, after approximately two months, caused irregularities which were quite noticeable and had to be repaired, whereas the diced grafts lent themselves to smoother moulding. Peer used this method for repair of defects of the skull, in reconstruction of the ear, and also recommends it to fill depressions over the malar bone to elevate the depressed

floor of the bony orbit. They form an ideal filling substance for a deep depression in the mastoid resulting from an extensive simple mastoidectomy.

Peer<sup>11</sup> presents an exhaustive review of plastic surgery for 1942.

**Fingertips**—Zadik<sup>12</sup> discusses methods of skin replacement after traumatic amputation of fingertips. It is believed that healing by granulations and edge epithelialization is not the method of choice. The indications favor graft or flap repairs. These are discussed and tables of results are given.

**Face and Mouth Defects**—Canon<sup>13</sup> outlines the use of remote flaps in repairing defects of the face and mouth. Repair of large, full-thickness defects of the cheek, nose, or palate can be carried out by the use of remote flaps. The forehead flap is useful in replacing tissue loss of the nose, cheek, or lips.

A flap from the inner surface of the upper arm is generally useful for repairs about the face. When used for repairs about the mouth, the flap is tubed to insure greater cleanliness and to diminish the risk of infection.

**Skin Knife**—Marcks<sup>14</sup> added an attachment to the Blair-Brown skin knife

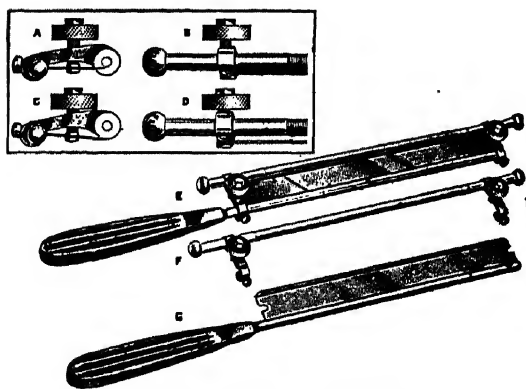


Fig. 5—The calibrated skin knife.  
(K. M. Marcks: Mil. Surgeon.)

which allows calibration of the skin graft. This calibration is not measured in fractions of an inch, but is placed on either

end to assure the operator that his graft will be of equal thickness throughout.

## FRACTURES OF THE MANDIBLE

**Fixation**—Winter<sup>15</sup> discusses fracture of the mandible and reports on application of the Roger Anderson Skeletal Fixation Appliance. The patient is operated upon under general anesthesia

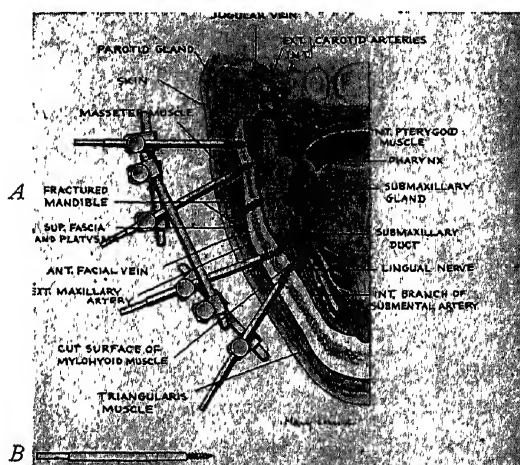


Fig. 6—A, horizontal section through the mandible at the level of the insertion of the pins; B, Winter pin with circumscribed marking. (Winter, L.: Am. J. Surg.)

(endotracheal route) or local anesthesia. The area of the face, if male, is thoroughly shaved and cleansed with tincture of green soap. The site and directions of the fractures are transposed to the external surface of the skin by indelible pencil or gentian violet markings. The inferior border of the mandible is palpated and just above it, about one-half inch on either side of the fracture line, marks are made for the points of insertion of the pins. Care should be taken to avoid the external maxillary artery, inferior alveolar canal, and mental foramen.

The area of operation is painted with tincture of merthiolate. The body and face are draped, leaving exposed only

the field of operation. With a Winter pin secured in a hand drill the skin is punctured with a straight jab until contact with the bone is reached. It is not advisable to turn the point through the tissue since the muscle and fascia would become entangled in the threads of the pin and make entrance and fixation in the bone difficult. With proper support to the fractured fragment, a slow hand drilling process is performed. The pins are inserted at approximately 70 degrees to each other. This affords a greater contact with the cortical layers of the mandible and so insures firmer fixation of the pins. Once entrance into the bone is made, it is possible digitally to feel the grip that the pin is making in the bony substance. The rotation is continued until the  $\frac{3}{8}$  inch marking on the pin has been reached and then, if further rotation is believed necessary, it can be continued. This process is repeated with the second pin. Single pin clamps are then applied to each pin, at an equal distance from the skin surface, usually about  $\frac{1}{2}$  inch. A rod is fastened through the respective openings in each clamp. In the middle of the rod a double clamp should be applied.

The bolts of each clamp are then tightened to insure that the unit is secure. This constitutes one Frac-sure unit. This procedure is duplicated with the third and fourth pins on the opposite side of the fracture and the second Frac-sure unit completed. With the occlusion of the teeth and the palpation of the inferior border as a guide, reduction of the displaced fracture is accomplished. While this is securely held in place, the fixation rod is passed through the respective openings of the double clamps, the bolts of the clamps tightened, and immobilization of the fracture attained. If, on radiographic examination, it is found the reduction has been incomplete, the bolts

of each double clamp are loosened and further reduction attained. The bolts are then tightened. If the articulation of the teeth is found to be faulty, due to the extent of the displacement, it has been found efficacious to resort immediately to the use of arch wires, in conjunction with rubber traction, to bring about the desired occlusion. This should be done immediately, for it has been found that patients are apt to rebel against the intermaxillary fixation after once experiencing the freedom of motion. This extreme displacement which is found difficult to reduce is usually encountered in cases in which the fracture is of a week or more duration.

**Uses**—Waldron, Kazanjian, and Parker<sup>16</sup> describe the evolution of the various methods of the skeletal fixation of fractures of the mandible. They came to the conclusion that this method will prove useful:

1. In badly displaced fractures of the edentulous mandible, particularly when comminuted.
2. In fractures behind the angle of the mandible when the posterior fragment becomes difficult to retain with the ordinary accepted methods.

In many of these cases, it will be wise to wire the remaining teeth in occlusion to assure further the stabilization of the fracture and the appliance. Occasionally, it may be impossible to close the teeth in occlusion because of bronchiectasis or other systemic conditions.

3. In certain types of mandible fractures, involving both upper and lower jaws, wherein dental splints, on account of the loss of many teeth, are not altogether satisfactory.

4. When no facilities are available for construction of a dental splint.

5. To the surgeon who does not have the services of dental surgeons. He will naturally find skeletal fixation more con-



Fig. 7—Typical injury ; showing loss of the greater part of the mandible, soft tissues about lip, and lingual tissues. (V. H. Kazanjian : J. Oral Surgery.)



sonant with his training, and will feel justified in its use.

6. In comminuted fractures of the mandible with destruction of a section wherein the isolated parts cannot be held adequately with dental splints because of the loss of teeth for use as anchorage.

from asphyxiation, the patient's tongue tending to fall back into the hypopharynx, since the forward muscular attachments and the hyoid are gone. An adequate air passage must be maintained at all times, the tongue being held forward by a safety pin through it or by turning



Fig. 8—Final photograph of patient (Case 1) previously shown in Fig. 7.  
(V. H. Kazanjian: J. Oral Surgery.)

(The same appliance could be used in case bone grafting should become necessary.)

**Extensive Loss of Mandible**—Kazanjian<sup>17</sup> outlines the treatment of extensive loss of the mandible and its surrounding tissues. Control of hemorrhage and shock is the first step. A great danger in the loss of the mandible is

the patient on his stomach in order to allow gravity to pull the tongue forward. An artificial airway similar to one used in general anesthesia can also be introduced. Apart from the control of hemorrhage, surgical interference in the early stages is limited to thorough cleansing by irrigation and débridement. Later the patient is encouraged to keep drainage



away from the hypopharynx by aspiration or the use of a suction machine. This is important to prevent bronchopneumonia. The patient must be well nourished and since he cannot chew and can swallow only in a restricted fashion, he must be fed by a nasal tube of small caliber so as to cause the least discomfort. As soon as local conditions are sufficiently favorable, usually in from eight to ten days after the injury, temporary splints should be adjusted so as to hold the remaining portions of the mandible in position. At this stage the fragments of bone are still loose and are therefore easily manipulated. If treatment is postponed, the gradual pull and shortening of the masseter and pterygoid muscles will cause difficulties in the proper appliance of the splints.

Kazanjian has found two types of splints to be simple and efficient:

1. If there are teeth on both sides of the jaw, third molars for example, a heavy band and bar splint is made. The bands are like strong orthodontic bands and the bar is much like a lingual bar, passing around at the imaginary cervicolingual margin of the incisors, with a T at the median line. A removable vulcanite splint fits over this arch.

2. If no teeth are available, a metal plate is bent to a U shape, modeling compound is added, and an impression of the remaining alveolar ridges is taken. The same compound bears the imprint of the opposing teeth. Thus, there is lateral and vertical control of the mandibular segments. The splint is removed from the mouth, trimmed, corrected and smoothed, and is then reproduced in vulcanite or plastic material. A buccal furrow between the cheek and remaining portions of the alveolar process of the mandible is maintained by adding a flange to the temporary splint.

Before operation on the lip and chin it is necessary to construct a prosthetic appliance to which the patient becomes accustomed. This appliance is held in place by the remaining teeth, by the alveolar ridges, or by the upper teeth in occlusion. Its bulk represents the lost bony tissue, especially at the symphysis. The prosthesis is made in three sections to facilitate removal, cleansing, and readjustment in the mouth.

To cover the soft tissue defect the author has been able to close it by swinging two large flaps from the remaining parts of the lip, cheeks, and side of the neck, and advancing these flaps so as to bring them over the prosthetic appliance. These flaps have the advantage of including muscular tissue from the orbicularis oris, and thus give later control of the lower lip by the patient. The provision of a complete epithelial lining for the buccal surface was more difficult. Usually there is enough mucous membrane to line the upper part of the lip, but in order to provide for the deep pouch in which the denture must lie, a flap of skin is turned up from the neck. This method usually suffices if a non-hairbearing portion of the neck can be utilized. However, this is often not the case, and then a flap must be raised from the side of the chest where there is no hair; it should be tubed and raised to form the epithelial lining. This, of course, is much more hazardous because of the length of the flap and its relatively poor blood supply.

The author considers the foregoing procedure as semifinal, preceding the reestablishment of the bone continuity of the mandible by bone grafting. Fortunately, our present day technic for the transplantation of bone has progressed far enough to make this final step practicable. However, it cannot succeed un-

less the recipient area and the tissues surrounding the skin are vascular and free of dense scars. If, in certain cases, bone grafting is for some reason not advisable, it is gratifying to know that these patients are able to masticate food tolerably well on the remaining stumps of the mandible.

without removal. The third, consisting of a rubber sponge covered with a condom, is worn until all danger of contracture of skin graft has passed. This mould may be easily removed and reinserted by the patient. All moulds described remain in place without the aid of an external brace or support.

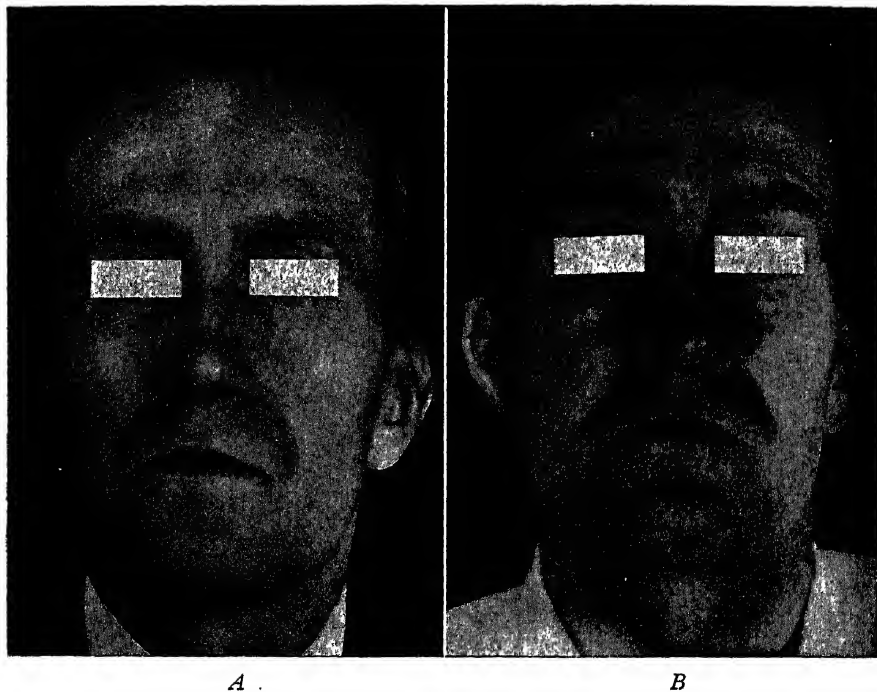


Fig. 9—Reconstruction of auricle following total loss due to trauma. (Berson, M. I.: *Am. J. Surg.*)

### ARTIFICIAL VAGINA

Adams<sup>18</sup> describes construction of an artificial vagina in one operation whereby the newly formed cavity is completely lined with a thick split graft ranging from thin to medium. Three types of vaginal moulds are used. The first, which is covered over with a half thickness skin graft and inserted into the newly formed cavity immediately, is made of rubber sponge surrounding a wire framework. This mould is comfortable, very soft, light in weight, and affords an even and constant pressure on the skin graft. The second mould, made of acrolite and also light in weight, has multiple perforations permitting vaginal irrigations

### RECONSTRUCTION OF THE AURICLE

Berson<sup>19</sup> describes a method for complete reconstruction of the auricle. In the first stage, a preoperative model is made of the patient's normal ear, reversed, and placed along the temporo-mandibular region above and behind the external acoustic meatus, corresponding to the position of the auricle on the opposite side. With brilliant green dye, a line is drawn circumscribing the margin of the model to delineate the location of the future auricle. An incision is made through the skin over the marking and a flap is lifted from the cranial periosteum up to the external auditory canal.

A large cartilage graft is taken from the fused parts of the costal cartilages and carved according to the pattern. The graft is then inserted into the prepared pocket between the scalp and the temporomandibular fascia, and the skin above it is sutured under tension by interrupted silk sutures. In a second stage, which is performed four weeks later, a semilunar incision  $1\frac{1}{2}$  cm. posterior to the proposed helix is carried through the temporomandibular fascia. The skin cartilage flap is raised as far as the external acoustic meatus, care being taken not to cut into or expose the cartilage. The raised flap is now larger than the desired ear, due to the excess skin to be used for construction of the helix. The skin of the flap is undermined to a distance of 2 cm. from its external margin. This loose flap is curled and sutured on itself at the rim of the implanted cartilage to form the shape of the helix corresponding to that of the model ear. This produces a helix and lobule shaped according to the opposite ear. The raw surfaces behind the new auricle are skingrafted, the graft wrapped around a mould of dental compound.

### MASTOPEXY

Maliniac<sup>20</sup> gives a description of the arterial blood supply of the breast with relation to reconstructive surgery. In summarizing his findings, he states that the blood supply of the breast is derived from at least two and often three of the following main sources: (a) The internal mammary artery; (b) the thoracic lateral artery; (c) the intercostal arteries (aorta). The most frequent combination is that of the internal mammary artery and the thoracic lateral artery (50 per cent).

A balance is usually maintained between the two main internal and external

vascular pedicles. The internal mammary artery is always present. In approximately 55 per cent of the cases, the thoracic lateral artery has an equal part with the internal mammary, and in 13 per cent a predominant part in vascularization of the gland, areola, and nipple.

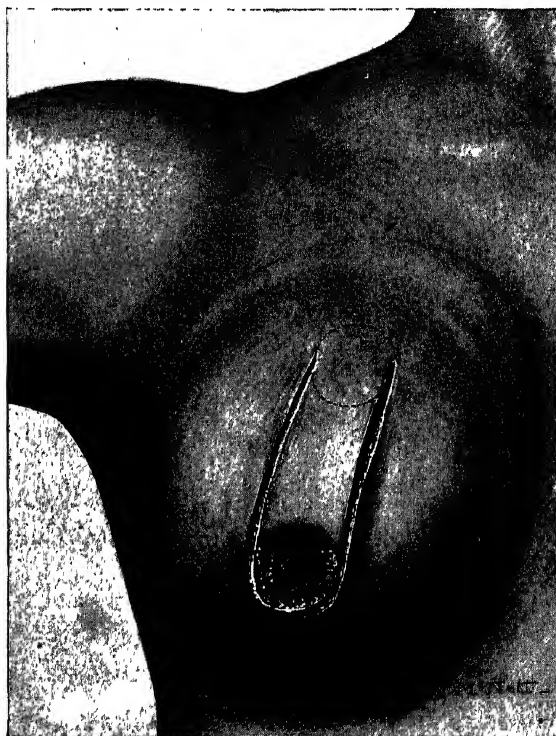


Fig. 10—The point to which the areola is to be transferred is marked with a drop of methylene blue. An ordinary medicine glass is used as a pattern and placed over this point and its rim is outlined on the areola. The most lateral and median points of both outlines are connected with each other by an incision. (May, H.: Surg., Gynec., and Obst.)

The ramification of the three main arteries of the breast participates in the formation of a superficial and a deep periareolar plexus, of which there are three basic types:

(a) The circular plexus (74 per cent) provides the safest vascularization for the nipple and the areola.

(b) The loop type (20 per cent) occurs when the thoracic lateral artery is predominant.

(c) The radial type (6 per cent) has periareolar ramification from the two main arteries, directed toward the nipple without anastomoses. Circular incision around the nipple in this type is likely to sever the blood supply and result in necrosis.

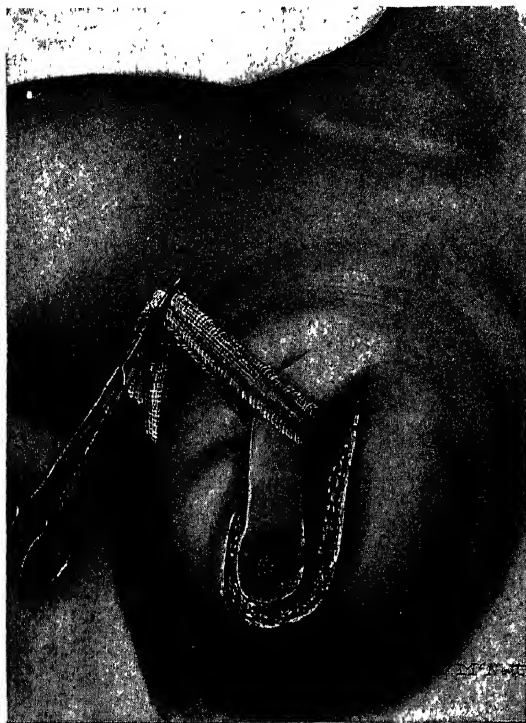


Fig. 11—Between both incisions the skin and subcutaneous tissue (not the areola) are undermined to form a bridge flap. Another incision is carried around the lower half of the areola. Note the outline of curved incision in lower half of breast. (May, H.: Surg., Gynec., and Obst.)

As it is impossible, prior to operation, to visualize the type of vascularization present in the living person, all surgical procedures based on wide resections of the mammary structures with ligation of large vascular branches must be considered to involve the danger of necrosis.

The surgical procedure of choice must preserve the blood supply in all types of vascularization.

May<sup>21</sup> describes and illustrates reconstructive operations for correction of various forms of hypertrophic and atrophic breasts. For moderately hyper-

trophic breasts, the one-stage operation after Lexer is recommended. For large hypertrophic breasts, the author devise a two-stage operation to safeguard the blood supply of the areola. The principle of this operation consists in the formation of a bridge—or double pedicle flap—

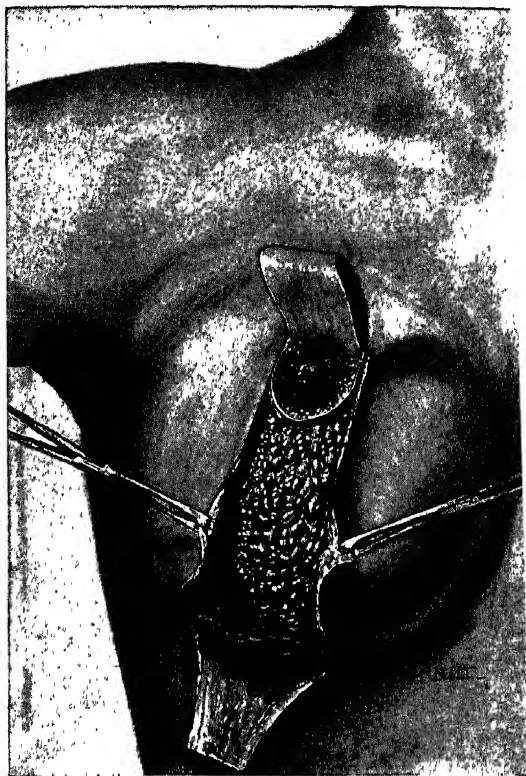


Fig. 12—After the undermining and separation of the surrounding skin the areola which is left in contact with its base is lifted upward and connected with the upper pedicle of the bridge flap with sutures. The next step consists of an incision of the skin below the areola in continuation of the upper cuts, but in diverging curves. The terminal points of the incisions should lie at least 1 inch above the mammary fold because the fold of the breast after reduction of its size becomes displaced upward. A triangular shaped piece of skin between both incisions is dissected downward to form a flap for later use. (May, H.: Surg., Gynec., and Obst.)

in which the distal pedicle is the areola; the latter remains anchored to its base. If the breasts are enormously large with poor circulation, a plastic amputation is preferable to a breast plastic. It has been feared that a plastic amputation may lead

to cystic degeneration and other disturbances; this can hardly be true in those breasts which are without function. A patient 30 years of age had very large breasts, both of which were cyanotic and displayed several flat scars from superficial ulcerations. She had one child, but did not lactate at that time. A bilateral

**Reconstructive Operation in Small Breasts**—If the breast deformity is unilateral, as it may be in postoperative cases, and the other breast is large, the large breast may be reduced by a breast plastic and some of the resected tissue transplanted into the small breast. If this is impossible, a fat tissue graft should

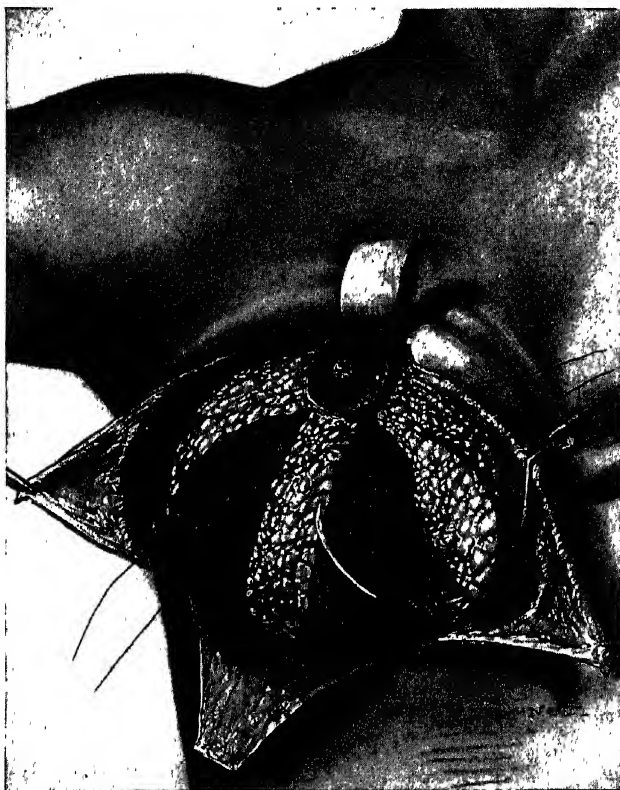


Fig. 13—Separation and blunt dissection of the skin from the lateral and median lower halves of the breast. The hypertrophic parts of the breast bulging laterally and median are grasped and excised in a wedge-shaped form. Thus, a center block of tissue is left to which the lateral and median wound edges are attached. This center part acts as a buttress and a carrier for important vessels. If it is still bulging it may be shaved off to the proper size. The lower sutures attach the breast and the pectoral fascia. (May, H.: Surg., Gynec., and Obst.)

plastic amputation was performed. Five years later she delivered another child; neither breast showed the slightest evidence of function. There are cases reported in literature where even in functioning breasts from which the nipples were absent, no pathological disturbances occurred during and after pregnancy. Some of the cases were followed up for many years.

be used. In genuine small breasts (hypomastia), hormone treatment should be given a trial (MacBryde). If it fails, fat tissue should be transplanted. The graft is preferably taken from the thigh. It is advisable to take the graft two-thirds larger than required to counteract degeneration and shrinkage. Furthermore, it is advisable to remove some underlying fascia with the fat tissue graft.



Fig. 14—The surrounding skin is now trimmed to conform to the lower half of the areola and breast, and is sutured together with two rows of sutures (subcutaneous and skin sutures). The bridge flap is separated in the same stage and the areola adjusted in place if clamping of the flap does not result in discoloration. If, however, discoloration becomes evident, this flap is removed two weeks later. (May, H.: Surg., Gynec., and Obst.)

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## THORACIC SURGERY

CHARLES P. BAILEY, M.D.

### "BLAST" INJURIES

We are seeing larger numbers of casualties among persons who were in close proximity to an explosion, in which, with

no particular external sign of violence, there are serious internal injuries. These are particularly marked in the thorax, in the abdomen, and less so in the cranial



cavity. The injuries to the lungs consist usually of both subpleural and parenchymal areas of hemorrhage. In many cases there are hemorrhagic marks on the lung surface following the outline of the ribs. In the abdomen there are areas of subserous and submucous hemorrhages in the alimentary tract. Occasionally a hollow viscus is ruptured, and then the usual sequelae appear. The brain substance and meninges may show focal hemorrhages, and blood spinal fluid may be present.

It is believed, especially from the work of Zuckerman,<sup>1</sup> that the injuries are produced as follows: in the vicinity of a high explosive detonation a very strong wave of force, a positive pressure or "percussion" wave, is set up which travels with the speed of sound in all directions, its force diminishing inversely with the square of the distance from the point of disturbance. This is followed by a much weaker "suction" wave which can never be greater than an absolute vacuum (15 lbs. per square inch less than atmospheric pressure).

The percussion wave is believed to produce the observed injuries. It may be completely deflected by any firm structure between it and the patient, and is much diminished by padding or armor surrounding the victim. When the percussion wave strikes a person, its effect is that of a blow. If one side of the thorax is turned toward the explosion, the bony thorax on that side strikes the underlying viscera a severe blow, causing the rib markings and hemorrhages. The other lung may show no damage.

The effect may be immediately fatal if the victim is close enough to the explosion, even though no missile has struck him. He may die a few hours later from internal loss of blood and pulmonary edema; or he may be weak, and perhaps

dyspneic a few days, and then completely recover.

The abdominal hollow viscera are also usually injured. It is felt that the air-containing organs (lungs, stomach, intestines) suffer most of the damage because the air in them is temporarily compressed by the pressure wave, and then violently expands during the negative pressure phase, injuring or rupturing the surrounding tissues and the walls of the containing organs. Since fluid and solids cannot be compressed, solid and fluid-containing organs suffer less.

Wilson<sup>2</sup> ascribes sudden death from blast injuries to the following causes: (1) Pulmonary hemorrhage; (2) cerebral deaths; (3) cardiac deaths—usually ventricular fibrillation; (4) air embolism.

Wilson and Tunbridge<sup>3</sup> describe the pathological findings in 12 cases of death from blast injuries suffered when a direct hit of a 1000-pound bomb occurred at the entrance of a bomb shelter. All cases showed rib markings on the lung surfaces and bilateral subpleural and parenchymal lung hemorrhages. Fifty per cent had hemorrhages into the abdominal cavity. One case had a ruptured aorta. All had 30 to 70 cc. bloody pleural fluid. No pneumothorax was observed in any case. Microscopically, widespread congestion of the alveolar capillaries with red cells and loose alveolar epithelium in the air sacs was noted. Occasional areas of lung emphysema with rupture of alveoli were seen in all cases.

Eve<sup>4</sup> believes that the suction wave, if it comes at the end of expiration, may temporarily evacuate the tracheobronchial tree of air, so that when the wave has passed, the epiglottis may be sucked back into the larynx and jammed there tightly, causing prompt asphyxia. He reports at least one case with autopsy showing this condition. Another person



standing beside the victim, who was presumably in a different phase of respiration, merely felt a catch in his throat at the time of the explosion, and was practically unhurt. Eve recommends that in such a case the epiglottis be forcibly retracted, or a large hollow needle or small trocar be inserted into the trachea to break the vacuum holding the epiglottis back in the larynx.

Blast injuries occurring to persons immersed in water are either due to a torpedo or bomb explosion nearby, or due to explosion of their own depth charges on sinking of their ship a certain distance below the surface. It is believed that the blast wave in water is purely a pressure wave, and that a negative or suction wave is impossible (Williams<sup>5</sup>).

Goligher, King, and Simmons<sup>6</sup> report 17 cases, 12 of which came to operation or autopsy; 9 had perforations of the small intestines. Both subserous and submucous intestinal hemorrhages were seen. Retroperitoneal hemorrhages into the loose areolar tissues behind the right colic flexure were seen in 10 of the 12 cases; 6 of the 7 autopsy cases showed lung damage similar to that of bomb blast in air.

All cases had been wearing pneumatic lifebelts at the time of injury, and the authors felt that the lung injuries were due to the slap of the diaphragms up against the thoracic organs. They feel that blast injuries in water chiefly affect the abdominal viscera, while bomb blast chiefly affects the thoracic organs. They estimate that the maximum injurious range is about 20 yards from the explosion and recommend that shipwrecked persons either rapidly swim away from the sinking ship or, if not feasible, lie on their backs in the water to lessen the effects upon the abdominal viscera.

Clark and Ward<sup>7</sup> use a large metal pipe bent in the form of a U-tube to sim-

ulate experimentally the conditions occurring in blast injuries in the water. In one side of the U filled with water were placed various anesthetized and unanesthetized mice, rats, and cats in wire cages. On the other side of the U was a floating plunger. Various weights were dropped from various heights upon the plunger to set up pressure waves similar to those due to explosives. These waves were rapidly transmitted to the immersed animals. Lesions similar to those reported in human cases of "immersion blast" could be produced at will and their severity controlled. The effects were directly proportional to the size of the weight used and the height it was dropped from, and inversely proportional to the size of the experimental animal used. They observed that the effects were greater on the lungs than upon the abdominal contents. These injuries were greater if the lungs were in a state of inflation than in one of deflation. The effects upon the central nervous system were least marked. It was observed that if air were injected by syringe into the animal tissues, this area would become the site of a hematoma after subsection to the blast injury. This suggests a temporary compression and secondary violent re-expansion of this air.

When animals were so suspended that their abdomens were under water but their chests out, the lungs escaped injury. If the lower half of the thorax was immersed, it was the only portion of the thorax in which pulmonary injuries occurred. In these cases the diaphragmatic surface of the lungs did not suffer as much as the sides, so it is doubtful if "diaphragmatic slap" is as important as previously considered.

Death in these animals was believed due to bleeding into the pulmonary tissue. These findings differ from those usually described in human "immersion

blast." The authors suggest two explanations. First, most survivors from a sunken ship will be wearing pneumatic life jackets, which hold the chest partly out of water and also lessen the effect of the pressure wave upon the thorax by their "padding" effect. Second, cases with severe blast injuries occurring on land fall down and rest physically until medical aid arrives, but those injured in water must continue to swim or hold onto wreckage or a raft until rescued. Naturally cases with severe pulmonary injuries cannot do this and are lost at sea. Therefore they are not recognized in the statistics.

Treatment of either type of blast injury is: (1) ***Prevention when possible***, as swimming away from a sinking ship, and protection of chest and abdomen by a heavy padding or rigid jacket. A solid object such as a tree or stone wall is an effective barrier to the percussion wave in air. Simply lying flat upon the ground will often protect against serious injury since the wave of force is partially reflected upward. Floating in water with the abdomen upward will greatly diminish the effects of immersion blast; (2) ***recognition of the condition and avoidance of unnecessary immediate surgery***; (3) ***rest***; (4) ***oxygen***; (5) ***plasma*** (very important).

## WAR SURGERY OF THE CHEST

Surgery in traumatic injuries of the chest may be divided into: (1) First aid; (2) definitive treatment. The first usually is concerned with arresting hemorrhage, correction of disturbances of cardiorespiratory physiology, and prevention of infection. The second is usually considered to mean actual surgical intervention of an injured chest in an attempt to restore the normal anatomy and functions of the thoracic structures. How-

ever, there is considerable overlap in these measures, so that a first aid treatment may well suffice to complete the cure.

There is often severe shock associated with chest injuries. Since the physiological disturbances to respiration and circulation may themselves produce further and progressive shock, it is essential that treatment of shock and the thoracic injuries proceed simultaneously.

Injuries of the thorax may be considered as (1) nonpenetrating and (2) penetrating, according to whether the missile actually penetrates the pleural cavity or not. An intermediate situation is sometimes present where a blow to the chest produces rib fracture, and a sharp fragment of the broken rib end penetrates the pleura and perhaps lacerates the underlying organs. This is classified as a nonpenetrating wound; although in many respects it is similar to those in the penetrating group.

**Nonpenetrating Injuries of the Chest**—These include lacerations and contusions of the soft parts; fractures of the ribs, simple, penetrating, compounded; fractures of the sternum, simple or depressed; crushing injuries of the thorax with multiple rib fractures and often disarticulations at the costochondral joints.

**Lacerations** of the chest wall may be simple, requiring only a suture or two. Large lacerations, especially badly contaminated ones, require adequate **débridement** and careful anatomical **repair**, if possible. Although the more extensive procedures usually require general anesthesia and fairly adequate surgical facilities, simple repairs of lacerations should be made at the earliest convenient moment to avoid further contamination and infection. The local use of **sulfanilamide** or **sulfathiazole** powder in these wounds is recommended by most

authorities. Daniel, Billings, and Crutcher,<sup>8</sup> in experiments upon dogs subjected to pneumonectomy and infected (pleurally) with hemolytic *Staphylococcus aureus*, found that *sulfathiazole* locally was much more effective than either *sulfanilamide* or *sulfadiazine* in preventing empyema.

*Contusions* are usually conservatively managed. Occasionally hematomas in the chest wall may require *aspiration* or *evacuation*.

*Simple fractures* of the ribs are usually treated by *adhesive strapping* and *injection of the intercostal nerves* posterior to the fracture site with procaine solution, 0.5 per cent, or alcohol, 30 to 60 per cent. Adhesive strapping should be nearly or completely around the thorax.

Penetration of the pleura by jagged rib fragments often lacerates the lung and may lead to pneumothorax, hemothorax, or both. Management is the same as that described for penetrating chest wounds producing similar lesions.

*Compounded fractures* of the ribs are treated by *débridement* and *primary wound closure* in most instances, with or without use of local *sulfonamides*.

*Fractures of the sternum* often occur at or near the manubriosternal junction. Most sternal fractures are transverse. The fragments may be displaced inward, and compress or lacerate the myocardium. In this case, or when there is slipping of the fractured ends with each respiration, either *suspension of the fragments by screws or pins*, or *an open reduction and fixation by plate or wiring* should be undertaken at once, if feasible.

*Crush injuries* of the chest may be accompanied by severe injuries of the underlying structures, especially if sharp fractured rib ends penetrate the pleural cavity. In that case the management is

that of a penetrating chest injury plus that of the crushed chest.

In crush injuries the multiple fractures of the bones cause a flaccidity of the chest wall. The situation is then somewhat similar to that seen in cases of large open pneumothorax. A paradoxical movement of the chest wall and lung occurs with every respiratory attempt. This markedly reduces the effective vital capacity of the good side.

The treatment consists of measures of general support, such as *transfusions* and *oxygen*, and some method of immobilizing the flaccid chest so the good side can maintain life. *Adhesive strapping* is helpful. *Lying on the affected side* is even better. In bilateral crush cases, the sternum or costal cartilages should be suspended by screws or towel clips and traction upward, preferably by a Balkan frame. Diaphragmatic breathing is then relied upon to maintain life.

**Penetrating Injuries of the Chest**—These may be divided into (1) closed and (2) open ones.

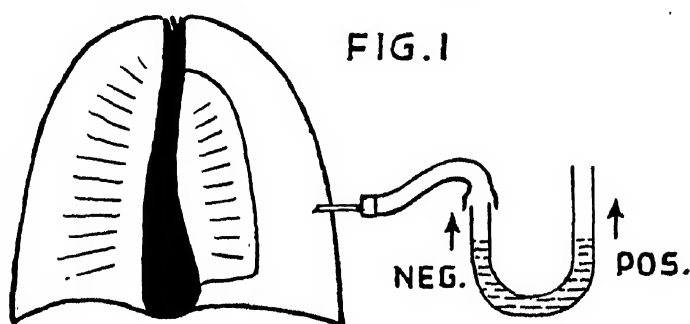
*Closed penetrating injuries* are those in which the sides of the wound, after the missile had passed, have fallen together so that there is no free ingress and egress of air into the pleural cavity. The danger of pleural infection is much reduced and the physiological disturbances to the respiratory mechanism is generally smaller than in open cases.

In these penetrating wounds one must look for pneumothorax, hemothorax, and later pleural infection. Pneumothorax is usually due to injury of the lung, but may be introduced during the momentary opening of the chest wall at the entrance of the missile.

Simple pneumothorax is the presence of air in the pleura at a pressure less than one atmosphere. For the sake of simplicity, although this is not strictly

true, it may be considered that this air merely takes up room in the thorax and thereby reduces the total vital capacity. In a healthy person this vital capacity is normally about eight times the tidal air requirements, so in these cases symptoms are seldom prominent (if the injury is unilateral). Treatment is not usually necessary, unless the patient is to be evacuated by airplane, in which case the *pneumothorax should be aspirated*, and facilities arranged for *administration of oxygen* during transit. Bilateral cases require *rapid deflation* of at least one side.

than one atmosphere (or "positive"), we are dealing with a "tension" pneumothorax. This usually means that the laceration of the lung leaks air in a valvular manner: air can escape from the lung into the pleura at inspiration or on coughing or straining but cannot re-enter the lung or bronchial tree on expiration. This process may stop after a certain amount of pulmonary collapse blocks the air leak, or it may continue to increase, gradually collapsing the good lung as well as the injured one by producing great deviation of the heart and



The simplest way to measure the pressure in a pneumothorax is by a glass U-tube with each arm 12 inches long, and the tube filled halfway with water. A piece of rubber tubing is connected on one end to the U-tube and on the other to a large aspirating needle which is then inserted into the pleural cavity. The fluid level in the glass tube will fluctuate with each respiration (Fig. 1). If its mean height is greater on the arm nearest to the patient the intrapleural pressure is less than one atmosphere ("negative"). If the fluid level is higher away from the patient the pleural pressure is "positive." If both levels are about the same, the pressure in the pleura is one atmosphere ("atmospheric").

If the pressure is atmospheric, it is probably gradually increasing toward the positive side. The patient should be carefully observed and frequent pressure readings made. If the pressure is higher

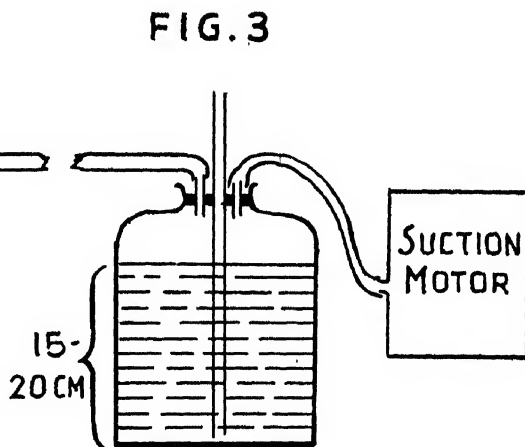
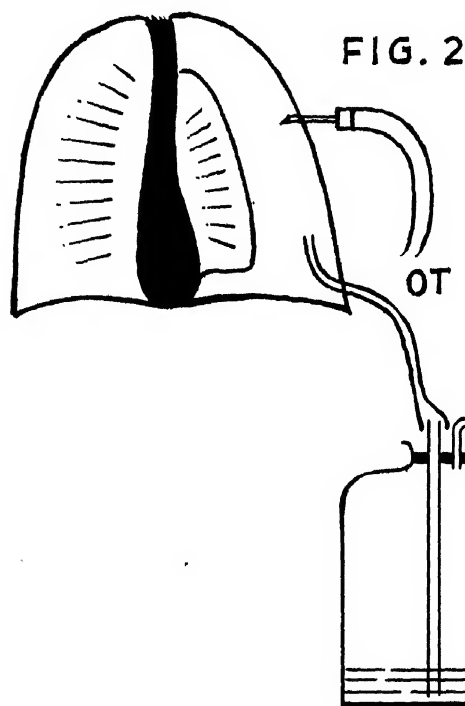
mediastinal structures toward the good side. Death may occur if this continues.

These patients must be watched very carefully with frequent checks of their pleural pressures. Increasing dyspnea, cyanosis, or signs of subcutaneous or mediastinal emphysema are indications for *immediate pleural deflation*. This may be done by a needle and a large syringe. However, it is most likely to recur, and a continuous type of deflation apparatus is desirable. The simplest of these is a large caliber aspirating needle inserted into the pleura and left there. Whenever the pleural pressure rises above one atmosphere the excess air will escape into the room. A simple way of fixing it in position is the application of a straight hemostat across the needle at the skin edge. The hemostat is then fastened to the chest wall by adhesive strapping.

The above method keeps the intrapleural pressure at about one atmosphere with a marked pulmonary collapse. If early reëxpansion is desired, a 4-foot sterile rubber tube should be connected to the needle and the other end placed about 1 cm. under a level of antiseptic fluid in a bottle or basin which is at least 18 inches below the patient. If the

lung leak is greater than the needle can effectively deflate. It must be remembered that a rapid reëxpansion of the lung may sometimes cause further lung laceration by direct trauma against the needle point in the pleura. Also there may be an increase in bleeding from the opening up (reëxpansion) of the lacerated area.

It is best to insert the needle into the anterior chest wall, usually second interspace midclavicular line, rather than posteriorly. In this position the patient can lie on his back; the bloody serum will not enter the needle; the needle point



fluid level is not that far below the patient, the developing negative intrapleural pressure may become high enough to suck the fluid back up into the chest. Usually the patient is in bed and the basin or bottle is placed on the floor. With such an apparatus, every effort of moving or straining by the patient forces air out of his pleural cavity into the rubber tube and out of it into the fluid. It then escapes into the atmosphere and cannot return to the system because the fluid above the end of the tube acts as a water-valve. Continuous deflation of the pleural space and reëxpansion of the lung result, unless (1) the needle becomes blocked by blood or serum, or (2) the

will be in the portion of pleural cavity which will be last occupied by the expanding lung. The needle may be left in place for ten days if necessary.

Where the air leak is too great for adequate aspiration by the needle method, or where it is also important to drain off fluid or hemothorax, a urethral or pezzar catheter may be inserted in the lower thorax. This is placed in the posterior axillary line through an intercostal stab, preferably by the use of a trocar and cannula. It is preferable that several extra windows be made in the intrathoracic portion of the urethral catheter, if it is chosen. The catheter is then also connected to a sterile water-seal system

(Fig. 2). Reëxpansion of the lung then cannot produce further laceration. Occasionally, it may be best to use a mechanical suction to help reëxpansion after several days. In that case the negative pressures must be controlled to be not over 15 to 20 cm. of water. This is most conveniently done by placing another bottle between the water-seal one and the source of suction (Fig. 3). A three-hole rubber stopper is used; 2 short glass tubes are inserted and connected by rubber tubing to the water-seal bottle and the suction, respectively. An open long glass tube is placed through the third hole to extend nearly to the bottom of the bottle. Water is now added to this bottle and the distance from the lower end of the long tube to the top level of the water is a measure of the constant suction pressure which will be maintained. Needless to say, the system must be airtight except for the open long tube. Whenever a rubber catheter is used for pleural drainage, it must be removed in four days and perhaps then replaced at another site to avoid admitting secondary infection.

Hemothorax occurs to some extent in all penetrating injuries of the thorax, and may be due to injury of intercostal vessels, internal mammary vessels, pulmonary parenchymal vessels, heart or great vessels. It consists primarily of blood but is increased after several days by a serous effusion which is a response of the pleura to irritation by the blood. Death may be caused by shock, loss of blood, or pressure (asphyxia) from the intrapleural bleeding. The presence of blood in the pleura predisposes to the development of infection.

*Injuries of the great vessels* are usually rapidly fatal and the cases can seldom be diagnosed or operated upon soon enough to save life. Schiebel<sup>9</sup> has re-

cently reported a stab wound of the pulmonary artery saved by prompt suturing, but that is exceptional.

*Injuries to the heart* are likewise usually rapidly fatal, due to arrhythmia or exsanguination except where pericardial tamponade occurs. Elkins and Cooper<sup>10</sup> describe the symptoms of pericardial tamponade as: collapse, unconsciousness, *fecal incontinence*, feeble or *absent pulse*, distended neck veins, profuse perspiration, low or imperceptible blood pressure, and a wound of the thorax of such location or type that cardiac injury would be likely. They note that incontinence is most rare in chest injuries except when cardiac tamponade occurs. They stress the value of immediate fluoroscopy of the heart in all suspicious cases. They consider the absence of visible pulsations of the heart to be pathognomonic. In questionable cases fluoroscopy should be repeated, and as soon as the pulsations cannot be noted, the pericardium should be explored.

The pathology in these cases is a wound of pericardium and heart with bleeding into the pericardium. A clot blocks the pericardial rent so that the blood cannot escape from the pericardium but must accumulate. This tamponades the cardiac bleeding and preserves the patient from an immediate demise. However, cardiac function is progressively impaired by interference with diastolic filling of the chambers and death usually results unless ***prompt surgery*** to repair the heart is undertaken.

Usually a long intercostal incision is made, the left pleural cavity is traversed, unless the wound is on the right, and the pericardium is opened. The bleeding from the heart is controlled by digital pressure until mattress sutures can be placed. Inclusion of coronary vessels in the sutures is to be avoided. Some

recommend placing apical traction sutures for better control of the organ before repairing the laceration.

Zerbini and Graver<sup>11</sup> report a case of a six-year-old boy injured by a fragment of iron which penetrated the right ventricle and lodged in the interventricular septum from which it could not be removed. They note the much greater frequency of injuries to the right ventricle than the left and the relatively better prognosis because the right ventricle maintains only a low blood pressure and so can be tamponaded more easily and with less effect on the general circulation than can the left. They quote Elkins as having good results in 22 of 38 such cases.

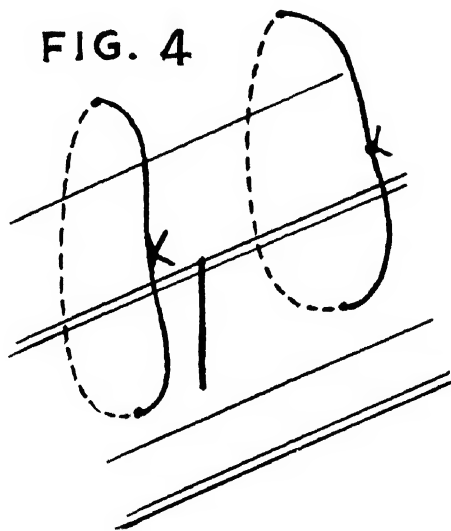
Blegen<sup>12</sup> reports 17 cases of wounds of the heart; 4 were cases of typical cardiac tamponade and were operated with 2 survivals. The mortality in untreated cases was 90 per cent. He advises *fine silk sutures through the epicardium and myocardium* but not the endocardium. Intraventricular clotting may follow the penetration of sutures into the cardiac cavities.

*Hemorrhage from the internal mammary vessels* is severe and usually will not stop until death ensues. Therefore, prompt surgical exploration of all penetrating wounds near the sternal margins should be routine, and then the bleeding will be recognized and controlled by *ligation of both bleeding ends, with or without resection of costal cartilages*.

*Hemorrhage from intercostal vessels* is variable in severity and may stop spontaneously, especially in wounds by blunt missiles, such as revolver or rifle bullets. However, a wound by a sharp-edged knife or a bayonet may cleanly sever an intercostal artery and not traumatize the surrounding tissues sufficiently to cause a hematoma and compression of

the cut ends. In these cases the wound should either be *surgically explored* to control bleeding or *prophylactic pericostal sutures of heavy ligature material* should be passed around at least the rib above the stab, both posterior and anterior to the possible point of vessel severance. The sutures should be removed in 3 to 4 days. These pericostal sutures should pass through the middle of the interspace above and return through the middle of the interspace below to avoid repenetrating the intercostal vessels in the groove under the inferior edge of the rib (Fig. 4). The sutures may be

FIG. 4



tied very tightly over a piece of gauze. This prevents cutting through the skin and keeps a tighter mass ligature about the rib and vessels.

*Bleeding from the lung* will stop when sufficient pulmonary collapse occurs to close off the low tensioned pulmonary vascular system. This collapse may be produced by either pneumothorax, spontaneous (traumatic) or induced, or it may be produced by hemothorax. However, blood is a less satisfactory compressive agent than air for the following reasons: (1) It collects at the base and a total hemothorax would be necessary to stop bleeding from an apical laceration.



(2) it exerts hydrostatic pressure against the mediastinum, causing greater dyspnea. (3) It is inelastic and cannot expand with enlargement of the thorax on inspiration. This permits some respiratory excursion of the injured lung until the hemothorax is great in amount. (4) Loss of blood necessary adequately to control bleeding may be dangerous (up to 2500 cc.), especially in a person who may have associated injuries, shock, or hemorrhage. Morelli in the first World War advocated *routine replacement of hemothorax by pneumothorax* to stop further blood loss. Tudor Edwards<sup>13</sup> has recently recommended that this be done. He has further pointed out that the presence of a large amount of blood in the pleura greatly enhances the likelihood of development of empyema, thickens the pleura causing delayed reexpansion of the lung, and prolongs rehabilitation. He reports 204 cases of chest injury, both civilian bomb and Dunkirk casualties, of which 44 were nonpenetrating. Of 24 cases of penetrating injury in which aspiration was done within 48 hours, only 3 or 12.5 per cent became infected. Of 180 aspirated after 48 hours, 20 per cent became infected. Only three cases in the 204 died, one of empyema.

He does not recommend air replacement after the first aspiration, since hematoma in the lung has ordinarily sealed off the bleeding, and it is advisable to reexpand the lung as quickly as possible to avoid having a free pleura to get infected.

Another reason to evacuate the pleura of blood rapidly is the occasional occurrence of sterile intrapleural clotting. This requires a thoracotomy for removal.

Smithy<sup>14</sup> has described the development of organization and chronicity with permanent lung collapse in certain cases of traumatic hemothorax which he estimates at 5 per cent of the total. How-

ever, he is not sure whether aspiration lessens the danger of this condition, as it may occur even then. He recommends *sterile thoracotomy and evacuation of the blood clots* after chronicity occurs. Elkins and Cooper,<sup>10</sup> on the other hand, in reporting 1132 penetrating chest wounds in civilians, have recommended that the blood be left for spontaneous absorption unless pressure symptoms or empyema supervene. They had a 1.76 per cent incidence of empyema, and a 6.36 per cent mortality.

The Morelli method seems more logical, and a very simple technic may be employed. With the patient supine or in Fowler position, a *thoracentesis* is performed using a 50 cc. syringe and either a 3-way stopcock or a snug-fitting, short piece of rubber tubing between the needle and syringe. Each time a syringe of blood is removed, a syringe of air is injected. The blood is collected in a sterile basin or flask, citrated, and stirred. At the conclusion of the procedure, it is filtered through gauze and may then be used for autotransfusion (unless the hemothorax is over 12 hours old, by which time changes in the blood may render its use for transfusion hazardous). If a manometer is available, the amount of air left in the pleura may be adjusted so as to leave a slight negative intrapleural pressure, say a 7 cm. water. Fluoroscopy may also be used to study the amount of pulmonary collapse. If neither of these facilities is available, air may be added at the termination of the thoracentesis until dyspnea occurs. This marks the limit of reserve vital capacity. At least 500 cc. of air should then be removed to leave a safe reserve. If the patient is unconscious, it is best at the end of aspiration to leave the needle open a few minutes so that an equilibrium is established between the atmosphere and the pleural pressures.

Then 500 cc. of air should be withdrawn to leave a safe respiratory reserve.

If blood or fluid increases in amount after a day or two, further aspirations need not be accompanied by replacement with air, and not more than 1000 cc. of fluid should be removed at a single sitting. This will have the effect of re-expanding the lung, which will not bleed at this time, and permits obliteration of at least part of the pleural space, lessening the danger of total hemithoracic empyema.

If further rapid accumulation of blood occurs after the induction of a large pneumothorax by this method and after control of possible chest wall bleeding, the bleeding is either coming from an extrapulmonary source such as an injured heart, great vessel, liver, diaphragm, or spleen, or the pulmonary bleeding is uncontrollable by pneumothorax (hilar injuries, adhesions preventing effective pulmonary collapse). The thorax should then be explored, providing that a competent anesthetist versed in positive pressure and controlled breathing technic is available. It is recommended that a *posterolateral incision be made and either the 6th or 7th rib be removed*. If the source of bleeding is the lung, it may then be sutured, using through-and-through mattress sutures if simple ones do not suffice. It is preferable that absorbable suture such as chromic catgut be used, since if empyema supervenes cotton or silk sutures will act as foreign bodies and may require another operation for their removal. *Lobectomy or pneumonectomy* should rarely be done except by a competent thoracic surgeon. If a surgeon not well versed in thoracic procedures feels it necessary to perform a lobectomy or pneumonectomy in such a case, it is advisable that he avoid the individual dissection of

the hilum or mediastinum and content himself with simple multiple through-and-through chromic mattress sutures of the lung as far as possible from the hilum. The lung may then be cut away distally leaving about a  $\frac{1}{2}$  inch cuff beyond the sutures. The pleural margins may then be inverted, but time is so important that this should often be dispensed with. An *intercostal catheter drainage* should be established through a posterior axillary stab wound, and connected by sterile tubing to a water-seal drainage system as described in the treatment of tension pneumothorax. The thoracic contents may then be dusted with *sulfonamides* up to 20 Gm. and the chest wall tightly closed without drainage other than the catheter. Pericostal sutures of heavy chromic gut may be used to approximate the ribs.

While the chest is open, other sources of intrapleural bleeding should be looked for. If there is a diaphragmatic rent, it should be enlarged and the abdominal viscera examined for perforation or laceration. Injuries of the liver may be a tunneling or grooving from the course of a bullet. Or there may be a fracturing of the liver substance, perhaps stellate in type. It is recommended that such injuries be *packed tightly with plain gauze* and that the end of the gauze be extended through the sutured diaphragm, across the pleural space and out through an intercostal stab wound in the chest wall. This may then be removed after several days without re-opening the thorax, and the *stab wound closed by interrupted sutures*. Intercostal catheter drainage with a water seal system should be used to favor lung reexpansion and avoid the necessity of frequent aspirations of accumulated fluid.

Injuries of the spleen usually require *splenectomy*, which is readily done

through the thorax. Gastric perforations may be easily repaired through this approach.

Any foreign bodies, such as bullets, clothing, or shell fragments, which are readily visible should be removed at this time. However, no undue time should be lost looking for small metallic bodies which are not easily found. Tudor Edwards<sup>13</sup> has shown that the incidence of empyema when small metallic foreign bodies are retained is scarcely higher than in control cases, being 23 per cent compared to 19 per cent.

Foreign bodies which are in the lung substance may be recognized by palpation and removed by *incising the lung tissue* where it is the thinnest over the object. Bleeding may be controlled by chromic mattress sutures. Since these objects may at times cause abscess formation, and since it is so easy to remove them when the chest is open, this should usually be done. However, exploration of the thorax is very dangerous in the absence of an anesthetist expert in this type of surgery, an experienced thoracic surgeon, and a properly equipped operating amphitheatre. No elective operation of this type should be done for foreign body unless these requirements are fulfilled.

King<sup>15</sup> has reported 22 consecutive cases of intrathoracic foreign body, 10 within the lung, 4 of which developed pulmonary abscess. The average convalescence required after removing the foreign body was 5 weeks. Therefore, such elective operations should not be done if the patient is about to be transferred to another hospital.

**Open wounds of the thorax** are those in which the wound in the chest wall is constantly open, permitting free ingress and egress of air to the pleural cavity. These injuries may be associated with loss of substance of the chest wall.

Intrathoracic injury is likely to be greater than with closed thoracic wounds.

*Bleeding* is usually greater because it is not tamponaded by pneumothorax or hemothorax, and because pulmonary bleeding is aggravated by every inflation of the lung on straining or forcible expiration.

*Infection* is much more likely because of the ease and prolonged time for dirt, clothing, and bacteria to enter the pleura.

*Asphyxia* is far more likely because an open pneumothorax causes greater disturbance of the physiology of respiration than a closed pneumothorax of equal size. The opening in the chest competes with the long natural air passage through nose, pharynx, glottis, trachea, and bronchus in permitting air to enter the thoracic cavity with each inspiration. If its area is five times the cross sectional area of the glottis, it is at least five times as easy for air to enter the thorax through that route as normally. The patient must then breathe several times as deeply to obtain as much effective lung aeration. Since this air entering the wound goes into the pleura, where it is not absorbed, it is useless. It also dries out the pleura, producing dehydration and shock. These figures are not strictly true since in many instances the mediastinum is partially fixed so that each lung and pleural cavity act relatively independently. There is also the factor of paradoxical or pendulum breathing. On inspiration, the good lung inflates, but if the chest wall and pleura on the opposite side are widely open, that lung does not inflate, since no negative pressure is effective upon it. On the contrary, this partially collapsed lung may further deflate, its air being drawn out by the inspiratory suck of the good lung. On expiration the reverse is noted. The good lung deflates and usually forcibly, since the accessory muscles of respiration are in play. The lung on the in-

jured side is blown up by the positive pressure created by this forcible expiration. This paradoxical breathing shunts a certain amount of air from one lung to the other with each breath. Since this air is rapidly depleted of oxygen and becomes high in carbon dioxide, the average alveolar air becomes lower in oxygen and higher in carbon dioxide. Both of these changes cause more dyspnea with even more forcible expiration and consequently worse paradoxical breathing. This vicious cycle may be broken by **closing the chest wall defect.**

The opening may be temporarily occluded by a towel or pack, preferably sterile. Further measures depend upon the circumstances as to surgical facilities, availability of competent anesthetist, and a trained thoracic surgeon. If a lacerated bleeding lung is present, it may sometimes be possible to suture or resect it through the existing chest wall defect. Since an airtight closure, such as would hold a pneumothorax, is difficult to produce in these cases, it is advisable to control all bleeding before closing the chest. Foreign bodies and clots should be removed from the pleura, and then the chest wall should be tightly closed after **thorough débridement.** **Sulfonamide** may be sprinkled into the wound and pleura, and an intercostal catheter water-seal drainage should be established. If the edges of the chest wall wound cannot be easily approximated over the defect, relaxation incisions may be made at some distance to permit complete closure. In some cases it may be necessary to swing a vascularized flap of skin and muscle tissue to cover the defect, allowing the new denuded area to granulate in. At times it is feasible to occlude the thoracic defect by suturing the lung to the edges of the wound. But if at all possible, the wound should be occluded by living viable tissue. The use of **oxygen under**

**pressure, infusions, and transfusions** may permit these maneuvers where they would otherwise be impossible. Failing to obtain a closure, the chest wall defect may be packed or occluded by dressings, and the certainty of a large open pleural infection accepted.

**Traumatic Emphysema of the Chest**—This is divided into subcutaneous air emphysema and mediastinal air emphysema. They are often combined.

*Simple subcutaneous emphysema* is usually of no great consequence; it is diagnosed by the swollen skin and the crackling feeling of air in the tissues on palpation. If it becomes extensive, it endangers life, and certainly should be promptly treated. It may be due to an underlying pneumothorax in which the air escapes through a rent in the parietal pleura. It may act as a safety valve in tension pneumothorax. In these cases the pneumothorax should be promptly removed by **syringe or continuous deflation**, unless its maintenance is necessary to prevent pulmonary bleeding. In some cases where pleural adhesions keep a punctured lung from collapsing, the air may leak directly through the tract of injury into the chest wall. Here it will be necessary to make incisions through the skin, fascia, and muscles to the layer of loose areolar tissue just outside the costal grille. Large rubber tubes are then inserted down to the level of the ribs, but not into the pleural cavity and no attempt is made to suture the incisions. Usually **two incisions**, on opposite sides of the pleural rent, and perhaps 2 inches from it, are adequate.

*Mediastinal emphysema* may also be due to the presence of a pneumothorax plus a rent in the mediastinal pleura. It may be due to laceration of the esophagus, trachea, or bronchus. In most cases it is probably due to laceration of lung tissue with interstitial air emphysema of

the pulmonary parenchyma. This air migrates along the sheathes of the pulmonary vessels to the hilum, where it enters the mediastinum and spreads up and down. Because of the presence of delicate vital structures in the mediastinum and the smallness of the space, it is very dangerous and may cause rapid asphyxia. Symptoms are: Substernal pain, oppression, increasing dyspnea to the point of orthopnea, distention of veins of face and neck, swelling of face and eyelids, pain and difficulty in swallowing.

Physical examination may reveal distant heart sounds and sometimes fullness and crepitus in the neck just above suprasternal notch and clavicles. Griffin<sup>16</sup> has described a peculiar clicking sound heard over the precordium synchronously with the heart sounds, and increased in certain phases of respiration.

X-ray, especially the lateral view of the chest, reveals the air in the mediastinum.

Treatment should be active in those cases which are severe enough to be diagnosed. Those resulting from lung laceration may be treated by incising the skin over the suprasternal notch and by *blunt dissection* between the ribbon muscles and through the pretracheal fascia, exposing the trachea. A firm rubber tube should be inserted to maintain the tract for deflation. If the trachea is lacerated, incision should be made to the point of injury if feasible and the rent sutured. If this is not practicable, a *tracheotomy tube* should be inserted, preferably below the thyroid isthmus (Nach and Rothman<sup>17</sup>), and maintained until healing has occurred. Lacerations of the major bronchi may be treated likewise.

Injuries of the esophagus are more serious because every attempt at deglutition forces air and highly infective saliva

into the mediastinum. These injuries may be considered as tantamount to a mediastinitis and should be treated as such as soon as the diagnosis is made. Either a cervical *mediastinotomy* or a lower dorsal one, or both may be made depending upon the estimated location of the esophageal leak.

The cervical mediastinotomy is made either anterior or posterior to the sternocleidomastoid muscle by displacing the carotid sheath and exposing the esophagus by blunt dissection. The dissecting finger may then be slid down behind the esophagus in the areolar tissue of the posterior mediastinum. Then a semi-soft rubber drainage tube is inserted. This incision will not permit adequate drainage in lesions or injuries extending below the sixth dorsal vertebra. These require a dorsal mediastinotomy.

The dorsal mediastinotomy is performed, on the injured side; on the right if the perforation came from within (swallowing of chicken bone, esophagoscopy, etc.). Two-inch segments of two ribs are removed from the tips of the corresponding transverse processes, laterally. Extrapleural dissection is begun and extended medially, approaching and passing anterior to the bodies of the vertebrae, anterior to the aorta until the esophagus is reached. The dissection is then extended up and down posterior to the esophagus. If the rent is seen it may be sutured with interrupted silk sutures. Semi-soft drainage tubes are used, and the wound is not sutured.

**Summary** — The treatment of chest wounds should generally be conservative. Elkins and Cooper<sup>10</sup> have suggested the following definite indications for surgical intervention: (1) Open sucking wounds; (2) stab wounds of the heart; (3) compression or "tension" pneumothorax; (4) extensive subcutaneous or mediastinal emphysema; (5) severe hemor-

rhage from intercostal or internal mammary vessels; (6) large lacerated wounds of the lung; (7) wound infections; (8) empyema.

It is probable that empyemas in traumatic cases had best be treated early by repeated aspirations by syringe, or by closed intercostal catheter drainage. Once they are frankly purulent and walling off of the pleura has occurred, it is probable that open rib resection thoracostomy is most practical. Once adequate open drainage is established, it is of the utmost importance that the tube should not be removed until the pleural space is completely obliterated. Edwards<sup>18</sup> considers too early removal of the drainage tube to be the foremost cause of persistent sinuses and chronic empyema.

Abdominothoracic injuries are very serious and present a varied symptomatology. These may refer to the abdomen or thorax, or both. If they are diagnosed as such, surgical intervention should be undertaken as soon as the patient's condition permits, and the route of exploration will depend largely upon the familiarity of the surgeon with abdomen or thorax, and also upon the predominance of symptomatology relating to these respective regions. If the wound is in the lower thorax, the likelihood of diaphragmatic dome injury is great. Combined injuries on the right usually mean laceration of lung and the upper portion of the liver. Since the upper surface of the liver cannot be well exposed from the abdominal approach, it would seem that the choice of approach on the right in these cases should usually be transthoracic, perhaps through the bed of the resected ninth rib.

On the left the choice is not so definite. Yet, remember that most of these injuries would involve the lung, diaphragm, and one or more of the viscera just beneath the diaphragm—stomach,

colon, spleen. These organs all lend themselves to easy surgical attack through the thorax. If the ninth rib is resected, and insufficient exposure is obtained, the anterior edge of the wound can easily be extended downward so that a true combined abdominothoracic incision is produced.

A good sign of gastric perforation is true hematemesis occurring shortly after a penetrating chest injury.

Tropea,<sup>18</sup> in treating war casualties in Tunisia, has observed a case of true tension pneumothorax in an abdominothoracic injury with perforation of the stomach and a valvular type leak of air through the torn diaphragm into the pleural cavity. He has also observed two cases of paradoxical breathing where no open injury of the parietal chest wall existed. There was a large diaphragmatic defect and also an abdominal wound in each case—permitting free ingress and egress of air to the pleural cavity on every respiratory effort. He recommends primary exploration through the thorax under positive pressure anesthesia, since abdominal exploration in these cases may prove too severe a strain on the partially asphyxiated patient.

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## DISEASES OF THE LUNG

### Agenesis of the Lung

Gartside<sup>19</sup> reports a case of agenesis of the left lung in a seven-year-old boy with congenital anomalies of the cervical spine, a left cervical rib, and a shrunk lung rudiment on the left side. He was able to find 37 cases of complete or nearly complete agenesis of the lung reported in the literature. In these the left lung was absent 23 times. It is believed that agenesis of the right lung is more of a handicap to prolonged life than agenesis of the left. Bronchography reveals the true condition.

**Etiology**—One of the primary divisions of the lung bud does not develop normally but either becomes a blind bronchial sac or a very small rudiment of lung tissue. This latter may become aerated in some cases.

### CONGENITAL CYSTIC DISEASE OF THE LUNG

The next stage of defective development is the formation of congenital cystic dilatations. A large cyst may replace an entire lung, a lobe, or a bronchopulmonary segment, or there may be multiple small cysts throughout a part or all of the pulmonary parenchyma. These cysts usually are air-containing, have flattened or cuboidal epithelium, are very thin walled, and usually have a bronchial communication. They may contain fluid or fluid and air. Occasionally a high intracavitary positive pressure develops in these cysts, causing great enlargement and symptoms due to displacement of and pressure on the other intrathoracic organs. This may require emergency *deflation* or *extirpation*. Fisher, Tropea, and Bailey<sup>20</sup> reported a successful emergency *bilobectomy* done on a 30-day-old infant because of impending asphyxia.

These cysts may rupture, causing a spontaneous pneumothorax (commonest cause in children). Such pneumothoraces may also give serious pressure symptoms, and may be persistent or recurrent.

Rumel<sup>21</sup> reports four cases treated successfully by surgical measures. One was cured by *local excision* of the cyst. One case was cured of recurrent pneumothorax by simple *poudrage of the pleura* with iodized talc. This produced pleural adhesions which prevented any further pulmonary collapse. The other two were subjected to right and left *pneumonectomy*, respectively.

These cysts may become infected and then resemble lung abscess or empyema. Frequently they require drainage but usually will not heal because the epithelial lining prevents granulations and obliteration of the cavity. It is necessary in these cases to excise completely the lining of the cyst before a cure can be expected. It is advisable in any case of subacute or chronic empyema, in which drainage and constitutional symptoms become very slight but where the cavity remains constant in size, to perform a *thoracoscopy*. If the lining of the space is seen to be pleura covered by granulations, the case is an empyema. If irregular trabeculations cross the space and bronchial openings can be seen, it is probably an abscess cavity. If there is a smooth, thin, epithelialized covering in a smooth-walled cavity, it is probable that the cavity is the wall of a congenital pulmonary cyst. Occasionally, abscess cavities may become epithelialized and cyst-like, and then require similar treatment. If hair can be seen on thoracoscopy the cyst is a dermoid.

Marshall and Cookson<sup>22</sup> recently reported autopsy findings on an eight-months-old child with a thin-walled cyst located behind the tracheal bifurcation and communicating with the left main bronchus. It was lined with tracheal type mucosa. Such an entity is also an example of maldevelopment of the lung buds, or perhaps of a supernummary one. It is called a tracheobronchial cyst.

Treatment in these cases of pulmonary agenesis, pulmonary cystic disease, and cystic tumors arising from the tracheobronchial tree varies greatly in the individual case. It would seem that *thoracoplasty* might be indicated in some cases of pulmonary agenesis to prevent extreme mediastinal shift leading to destructive emphysema of the good lung.



**Resection** would be indicated if the underdeveloped lung tissue became infected.

In most cases of pulmonary cystic disease, no treatment is indicated. Development of infection in the cyst produces a condition similar to lung abscess and requires similar treatment. Tension cavities may give severe pressure symptoms and may be deflated by a drainage tube. Later the cyst wall should be excised. Brown and Brock<sup>23</sup> advise a **permanent endocutaneous flap** in cases of large tension cysts. The cyst, or the lobe or lung containing it, may be primarily resected. Rigler<sup>24</sup> advises **extirpation** even in acutely infected cysts.

Tracheobronchial cysts should probably be excised as soon as diagnosed to avoid pressure, infection, and possible malignant changes.

Benson, Evans, and Zuelzer<sup>25</sup> report a case of *Echinococcus* cyst of the lung which had developed a bronchial communication. Air existed between the capsule and the true cyst (perivesicular pneumocyst). When bronchial communication occurs, hooklets or bits of the membrane of the cyst wall may be found in the sputum. These lesions are rare in the United States. A one-stage **enucleation** operation is preferable to lobectomy. Drainage is unsatisfactory.

### Hemangioma of the Lung

There have been only seven such cases reported in the literature. Patients usually have severe clubbing of the fingers and may show polycythemia. Hepburn and Dauphine<sup>26</sup> report an eighth case, right-sided disease in a 23-year-old female. She had advanced clubbing of the fingers, cyanosis, and polycythemia even to 9,000,000 red cells. She was successfully treated by total **pneumonectomy**. Following this, the cyanosis improved almost at once. Later the polycythemia disappeared.

One must remember that the effect of such a lesion is to produce a large arteriovenous shunt of the pulmonary system. If the disease is extensive, pneumonectomy probably is the best type of surgery.

### BENIGN TUMORS

Primary benign tumors of the lung or the bronchi are rare. Fibroma, chondroma, and osteochondroma may occur. The commonest of the so-called "benign" group is the bronchial adenoma. These may cause persistent hemoptysis. They arise usually from the main bronchi or their major divisions and so are suitable for diagnosis by bronchoscopic biopsy in most cases. They usually cause trouble by obstructing the bronchus with ensuing atelectasis of that bronchopulmonary segment. This in turn is followed by supuration and either abscess formation or bronchiectasis. **Bronchoscopic treatment** has been used widely in treatment of this condition. By removing the intrabronchial portion of the tumor, relief of obstructive symptoms is obtained. In most cases there is a considerable extrabronchial portion of the tumor, which cannot be removed bronchoscopically.

Some of these tumors look histologically like adenocarcinomas and there is considerable confusion in the literature regarding their proper classification. There have been several reports in the literature of local or lymph node metastases in these tumors, occasional reports of distant metastases. Anderson<sup>27</sup> has reported a recent case in a 40-year-old man with persistent productive (mucoid) cough for six months, associated with hemoptysis and asthmatic symptoms. Autopsy revealed an adenoma of the right main bronchus protruding into the trachea and a large metastasis to the liver.

Since cartilage and fibrous areas are not infrequently seen in sections of these tumors, we may perhaps liken them to mixed tumors of the parotid, and call them mixed tumors of the bronchus. They should be considered as at least potentially malignant. It would seem advisable that **complete resection** of these tumors should be undertaken as soon as the diagnosis is made. In most instances this would require lobectomy.

### Primary Carcinoma of the Lung

It is felt by most chest physicians that these carcinomas always originate in a bronchus, large or small, and therefore the condition should be called primary bronchiogenic carcinoma. Others maintain that a certain number of these tumors arise from the true pulmonary parenchyma (perhaps 15 per cent of all cases). This is a very important disease, since it is apparently the most common malignancy occurring today. Overholt<sup>28</sup> reports that 10 to 20 per cent of all cancer deaths found at unselected autopsy in large city hospitals are due to primary lung cancer. There is some question whether gastric malignancy exceeds it in frequency. Apparently there is a considerable increase in the incidence of the disease in recent years. Unselected autopsy studies done in large hospitals have shown a far greater frequency of this disease recently than comparable autopsy series 20 years ago. Macklin<sup>29</sup> suggests that there is a real increase in the incidence of pulmonary carcinoma but that it is smaller than the vital statistics and autopsy reports would suggest. Other than the factor of missed diagnoses in previous years, the following factors in the apparent increase must be considered: (1) People live longer and so reach the cancer age; (2) autopsies are nowadays more common in institutions for the care of tuberculosis and

other chronic diseases; (3) the pathologist is keenly aware of the frequency of this disease and is looking for it; (4) fewer cases are now being called metastatic carcinoma of the lung.

**Etiology**—This is unknown. It may be due to some chronic irritation, as from inhaled dust or chemicals. Tobacco smoking has been indicted at times. The disease usually occurs in the "cancer age"—from 40 to 65. However, it is not rare in the aged, and Hauser<sup>30</sup> has recently reported a typical case in a 17-month-old infant. It occurs four or five times as commonly in men as in women. Blake<sup>31</sup> has reported its occurrence in association with a foreign body in the affected bronchus. Warcalde<sup>32</sup> has shown the association of bronchiogenic carcinoma of the lung with pulmonary tuberculosis in four cases.

**Pathology**—The histological pattern in these tumors has been variously classified. Most pathologists consider carcinoma of the lung to fall into three general groups, each making up about one-third of the total: (1) Squamous-cell or epidermoid types, which tend to be least malignant; (2) adenocarcinoma, which tends to be more malignant than the epidermoid types; (3) undifferentiated or round or oat cell types which are extremely malignant. Konzelman<sup>33</sup> feels that serial sections will often reveal all these different types in the same individual tumor, and that there is merely a preponderance of one type in each case.

Another method of classifying these tumors relates to their location with respect to the pulmonary hilum. Approximately 75 per cent of these tumors arise from the major bronchi and so are central in location. About 25 per cent arise in the peripheral portions of the tracheobronchial tree or lung.

The central type produces in one of the larger bronchi either ulceration fol-

lowed by stenosis, or growth and fungation into the lumen, or both. The early invasion of the bronchial wall sets up an irritant reflex cough with or without mucoid sputum. These tumors bleed easily, frequently causing persistent or severe hemoptysis. By further growth or stenosis bronchial obstruction is produced. Early this is partial, and unilateral (or bilateral) wheezing is produced. There is always a stage of obstructive emphysema with shift of the mediastinum away from the affected side, but this phase may be short and is often overlooked. At this time dyspnea is first noted, caused by poor aeration of the blood circulating in the affected pulmonary division, or by mediastinal shift, or by reflex bronchospasm (asthmatic breathing). Later more complete obstruction sets in. Atelectasis of the affected pulmonary division finally occurs. If the main bronchus is occluded a massive atelectasis occurs and severe symptoms appear with mediastinal shift toward the affected side. Infection may set in either in the stage of partial or complete bronchial obstruction. It appears as a pneumonitis which is often mistaken for an ordinary pneumonia and treated by *sulfonamides* and the usual supportive measures. It may be recurrent, or there may be a breakdown with abscess formation in the lung distal to the carcinoma. This abscess formation is different from that due to central necrosis of a large pulmonary malignant mass. With less severe infection or less complete obstruction, the pulmonary segment distal to the lesion becomes the site of extensive bronchiectasis. These associated inflammatory lesions may mislead even very experienced radiologists.

The peripheral type tumor grows as a spherical or ovoid mass in the outer lung field and often produces no early symptoms. Apparently some of these tumors

can last for a long time (in a personal case at least three years), without seriously inconveniencing the patient. This is not the rule, however. Extensive mediastinal lymph node or distant (bone, liver) metastases often occur before symptoms directing attention to the lungs appear. Because of the bronchiogenic origin of these tumors, hemoptysis is common and very often the symptom which leads to proper study and diagnosis. Since the rounded shadow on the x-ray film is similar to that with a single mass metastasis from extrapulmonary malignancy, there has been great stress laid upon the differential point of hemoptysis indicating a primary tumor. Freeland and Greenfield<sup>34</sup> have recently reported two cases of single mass metastasis to the lung, one from a thyroid, and one from an ovarian tumor, both presenting hemoptysis. King and Castleman,<sup>35</sup> in a review of 109 autopsied cases of metastatic pulmonary malignancy studied at the Massachusetts General Hospital, found that in 18.3 per cent bronchial invasion by tumor could be shown histologically (either direct metastasis to the bronchial wall or erosion of a mass malignancy into a bronchus). Only four of the 109 cases had hemoptysis. Since many of these cases presented very numerous metastatic nodules in the lung, and since only four of the entire series had hemoptysis, it would seem that hemoptysis occurring in a case with a single mass in the lung would still be good presumptive evidence of the presence of a primary neoplasm.

The incidence of secondary inflammatory disease in peripheral malignancy is much lower than in central, probably because only small, relatively sterile, bronchi can be occluded by the growth. Occasionally, central necrosis and infection occur within the tumor mass. This may then show a cavity and a fluid level and

simulate an ordinary pulmonary abscess. The greater thickness of the abscess wall will suggest the true nature of the lesion.

Extension of the peripheral tumor to the pleura may produce obliteration of the pleural space at that point, with extension into the contiguous parietal, mediastinal, or diaphragmatic region. Or it may cause pleural exudation and the development of a large pleural effusion, and collapse of the lung. At first the fluid is thin, clear, and straw colored. After weeks or months it becomes blood tinged, and occasionally purulent. Tumor cells can often be found in the sediment of this fluid. Widespread parietal metastasis is usually present by the time the fluid is first detected.

When a peripheral tumor is located at the extreme apex of the lung, it may extend up into the upper mediastinal and cervical region and give the classical signs of the superior pulmonary sulcus tumor of Pancoast (Horner's syndrome, brachial plexus pain, erosion of first rib or vertebra). If the tumor extends to the chest wall it may erode ribs and cause severe neuritic pain. Some of these tumors invade the vertebrae by direct extension.

**Symptoms**—These are variable and often misleading; they are absent in the earliest stages of the disease. It is most important that the physician be suspicious of every patient with pulmonary symptoms, especially if over 40 years of age. Cough is the most constant symptom, although often absent in the peripheral type. Hemoptysis is less constant but of great significance when present. Chest pain may indicate pleural or chest wall involvement and is usually of a persistent type. Dyspnea coming on rather suddenly in a person past 40, especially with wheezing (particularly if unilat-

eral) is suggestive. Chills and fever, weight loss, and weakness are often due to associated inflammatory disease and careful study is required in any case presenting them.

**Diagnosis:** (1) Clinical suspicion is the most important single element in prompt diagnosis. According to Overholt,<sup>28</sup> the average patient sees a physician within three months of the onset of symptoms, the physician waits three months before ordering an x-ray of the chest, and another three months elapses before the diagnosis is proven. Yet it is possible to prove the diagnosis in 95 per cent of the cases by methods readily available at present. Robertson<sup>36</sup> reports that 42 per cent of a series of 52 cases seen by him had been accurately diagnosed by the referring physician even before hospitalization.

(2) The upright PA x-ray film will reveal abnormalities in practically every case of malignancy often before any symptoms are present. Occasionally lateral or planigraphic or oblique views may be necessary. The diagnosis may still be in doubt if the lesion does not appear typical but the indication for further study is then apparent.

(3) Bronchoscopy will accurately diagnose and usually prove by biopsy practically every case of the central type. The peripheral type is not usually diagnosable by bronchoscopy, but even here it is possible sometimes to find bronchoscopic evidence of mediastinal metastasis (widening and fixation of the carina) or signs of extrinsic bronchial pressure.

(4) Exploratory thoracotomy in properly selected cases, and in good hands, is a safe and valuable diagnostic procedure. The characteristic feel of the tumor within the lung is usually sufficient for an experienced surgeon to make the diagnosis. If he is in doubt, a portion of lung tissue can be removed and immediately examined by frozen section method. At the same time the possibilities of complete surgical extirpation of the growth are considered, and if the lesion is operable, *pneumonectomy* may be immediately performed. In cases with much suppuration or bronchial secretion, exploratory operation is more serious because of danger of postoperative drowning or atelectasis.

Those are the generally recognized diagnostic elements necessary for proper management looking toward a cure. Other diagnostic measures of less or

auxiliary importance, perhaps purely for scientific purposes, are:

(5) Aspiration biopsy of the mass with a large needle under fluoroscopic guidance (preferably biplane). This requires a certain amount of skill on the operator's part. If the aspirated fragments reveal a malignant process, an exact tissue diagnosis is obtained in 35 to 70 per cent of cases. The measure usually is no great hardship to the patient. On the other hand, pathologists are often not familiar with this type of biopsy and hesitate to make a final diagnosis on such a small specimen. And there is always the danger of implanting tumor cells or infected material in the pleura or chest wall. Air embolism is always a possibility. If the case is inoperable, these considerations are of less importance; but if the case is operable, the finding of a positive aspiration biopsy points toward operation for hope of cure. And if a negative biopsy is obtained, exploratory thoracotomy with the hope of pneumonectomy is still necessary, since the negative report would not rule out malignancy.

(6) Examination of the sputum for tumor cells. This study has previously been considered useful only in far advanced lesions. However, Gowar<sup>37</sup> has reported that by Dudgeon's wet-smear method 64.3 per cent of his 93 cases had sufficient tumor cells in the sputum for definite diagnosis. Many of these were relatively early cases. He particularly recommends the method for cases in which the growth is masked by associated inflammatory disease. Ceballos, Bottini, and Escudero<sup>38</sup> have reported an early case diagnosed by this method and successfully treated by pneumonectomy.

(7) Finding of tumor cells in the sediment of pleural fluid in cases with large effusions is only of value from the scientific standpoint, since these cases already have had extensive malignant dissemination to the parietal pleura.

(8) Biopsy of axillary or other lymph nodes or of a portion of tumor eroding the chest wall are only of value to obtain an exact tissue diagnosis. These are nearly always already inoperable cases.

(9) *Artificial pneumothorax* by separating the lung from the chest wall may enable the clinician to differentiate between a mass within the lung substance and one in the chest wall or mediastinum. It is also a necessary preliminary for

(10) *Closed thoracoscopy*. By means of a thoracoscope introduced through a cannula in

an intercostal space, the parietal pleura and lung surface can be visualized. Biopsy of pleura or lung surface may be obtained through this instrument. Again these cases must be practically hopeless before a certain diagnosis can be made by this method. This is particularly valuable for diagnosis in cases of pleural effusion.

**Signs of Inoperability**—(1) Evidence of extension into a vital contiguous part, such as erosion of a vertebra; (2) distant metastases (brain, liver, bones, distant lymph nodes); (3) pleural effusion (this means extensive parietal metastasis); (4) paralysis of a recurrent laryngeal nerve as shown by vocal cord immobility on laryngoscopy; (5) phrenic nerve paralysis as shown by paradoxical movement and very high position of the homolateral hemidiaphragm; (6) Horner's syndrome (due to involvement of the inferior cervical sympathetic ganglion).

It will be noted that these last three lesions are nerve involvements. While it is true that pressure on a nerve may cause its paralysis, thoracic surgeons agree that involvement of these nerves in malignancy is practically always due to direct invasion by malignant cells. Since these nerves lie in the mediastinum, these lesions indicate mediastinal invasion. Occasionally the phrenic may be involved only in that portion which lies on the pericardium, and since the pericardium may be resected with the lung, this would not by itself contraindicate surgery.

**Prognosis**—Life is seldom longer than one year after the diagnosis is made unless complete resection of the lesion can be performed.

**Treatment**—The only treatment directed toward complete cure is *surgical excision*. It is generally considered that because of the crossing of lymphatics between the various lobes of the lung, nothing less than a *total pneumonectomy*

can be considered an adequate operative removal of pulmonary malignancy. However, practically all thoracic surgeons, either because of the patient's unsatisfactory general condition, or because of finding a very localized lesion, have on occasion done merely *lobectomy* or even *partial lobectomy*. A few good results have apparently been obtained thus. In general these lesser procedures must be considered inadequate.

*Total pneumonectomy* is surprisingly well tolerated in most persons. However, many of these patients are of advanced age and may have unrecognized cardiovascular or renal lesions. Hence, the mortality of pneumonectomy for carcinoma will probably always be high. It is about 20 per cent in good hands.

There are several very important points to be considered in carrying these patients through a successful operation to satisfactory recovery. First there is the problem of the patient's cardiac status. Johnson<sup>39</sup> considers cardiac weakness as the chief contraindication to surgery in technically operable cases, and advises that no cardiac case be operated. Courmand and Berry<sup>40</sup> have pointed out that it is impossible to predict whether cardiac failure will develop in any given case. There are two types of cardiac failure, both rightsided, if one does not consider operative shock as cardiac failure. One develops soon after surgery and is apparently related to the sudden hypertension produced in the pulmonary circulation due to ligation of one of the main pulmonary arterial branches. The other comes on after three to six months and apparently is related to the extreme mediastinal shift and emphysema of the remaining lung in Nature's attempt to obliterate the dead space remaining after pneumonectomy. This latter condition may be avoided by a phrenicotomy and

thoracoplasty on the operated side to obliterate the pleural space.

The sudden hypertension in the pulmonary circulation can probably be avoided if the affected lung can be collapsed by *pneumothorax* or other means for a sufficient length of time preoperatively to shut off its circulation appreciably, thus permitting gradual enlargement of the vascular bed of the other lung. The time factor is so important in malignancy that most operators dislike to establish a complete and prolonged pneumothorax prior to pneumonectomy for cancer even when pleural adhesions do not prevent it. Yet there is no doubt that removal of collapsed and functionless lungs, as in extensive bronchiectasis or post-thoracoplasty cases, is attended with far less disturbance to the circulation than sudden removal of a functioning lung.

Closure of the bronchus is of utmost importance in pneumonectomy, since total empyema follows a bronchopleural fistula. Rienhoff, Gannon, and Sherman<sup>41</sup> have reported an improved technique after extensive experiments upon dogs, and also in a large series of clinical cases. They recommend that: (1) The primary bronchus be amputated near the bifurcation of the trachea, leaving a short stump; (2) no crushing clamps or cautery be used; (3) as few sutures be used as necessary for airtight closure of the stump; (4) the sutures be a single row of mattress sutures encircling a cartilaginous ring; (5) the bronchial stump should be completely covered by mediastinal pleura.

They report only two bronchial openings in the past 27 human cases so treated.

The fifth of their suggestions is probably the most important one, since the relatively avascular bronchus, lined by mucosa and with walls of elastic car-

tilage constantly attempting to spring open (thus constantly cutting against the sutures), can hardly be expected to heal per primum. Any method of suturing or ligature should maintain an airtight stump for 10 to 14 days. In the meantime, a viable tissue, such as a flap of pleura or intercostal muscles, will become tightly healed to the mediastinal defect if properly sutured in place.

Another very important problem in pulmonary resection is the maintenance of proper circulation and fluid balance during and immediately after surgery. Blood loss in thoracic surgery is greater than generally supposed. White and Buxton<sup>42</sup> have shown that blood loss in classical thoracoplasty operations averages between 500 and 1000 cc. per stage, in lobectomies 1607 cc., in total pneumonectomies 1458 cc. This blood loss undoubtedly accounts for much of the operative shock formerly observed in these cases. Hence, modern thoracic surgeons usually operate with a constant intravenous infusion of fluid and/or blood running. This is a great factor in preventing shock, but the work of Gibbon, Gibbon, and Kraul<sup>43</sup> and Gibbon and Gibbon<sup>44</sup> has shown (experimentally) the danger of pulmonary edema after extensive lung resection when blood or plasma is given too freely. Saline or glucose solutions would probably increase this tendency. Drinker and Warren<sup>45</sup> have stressed the tendency of increased pressure in the pulmonary capillaries to produce transudate into the alveoli, and also the ability of anoxia to increase the permeability of the pulmonary capillary walls. Certainly the giving of excessive intravenous fluids would produce increased capillary pressure, and anoxia may very well be present either during operation or in the postoperative period. Ligation of large pulmonary arterial branches unquestionably increases

the pressure in the remainder of the pulmonary vascular system.

Maier and Cournand<sup>46</sup> and Adams, Thornton, Carlson and Liningston<sup>47</sup> have shown that anoxia seldom occurs during anesthesia competently given for intrathoracic surgery unless there are excessive inflammatory secretions from the diseased portions. However, they find that in the postoperative period there is at least transient anoxia in an appreciable proportion of cases, usually due to mechanical disturbances of respiratory function. This can be lessened by routine postoperative oxygen therapy.

It will be seen that in spite of the complexity of the problems concerned, that there is a solution for each one. Therefore, satisfactory results may be expected in the large majority of cases where these procedures are undertaken in adequately equipped and staffed centers. It will also indicate that these procedures should not be lightly undertaken by one inexperienced in these problems.

**Radiation therapy** is believed to offer no chance of complete cure in pulmonary malignancy. Perrone and Levenson,<sup>48</sup> in reporting on a series of 77 cases diagnosed by bronchoscopic biopsy, the majority of whom were treated by radiation therapy, note that all but one were dead within 18 months of diagnosis. The one living case had survived three years after pneumonectomy and was apparently well.

However, radiation therapy, usually in the form of deep x-ray, in selected cases will often give a reasonable degree of palliation. It is particularly effective in the less differentiated forms of malignancy. It should be used with caution in cases with much associated inflammatory disease.

**Bronchoscopic removal** of obstructing portions of the intrabronchial malig-



nancy is occasionally of palliative value in preventing damming up of infected secretions in the distal portion of the lung.

Palliative *drainage of pulmonary abscesses* occurring either distal to or within a necrotic neoplasm is usually to be condemned. True, the high fever and septic symptoms may be reduced and life prolonged, but the wound will not heal. Late fatal hemorrhage from the wound is common and is looked upon with suspicion by the laity. Eventual ulceration and fungation about the wound are usual, and often associated with extreme pain.

*Pneumectomy* may occasionally be indicated as a temporary palliative of high degree. Overholt<sup>28</sup> recommends it in certain cases. This is still a serious operation, and must be carefully considered before performing upon a case with no hope of complete cure.

### Pulmonary Abscess

**Definition**—Nontuberculous suppuration of lung tissue with one or more localized areas of necrosis resulting in pulmonary cavitation. The majority contain anaerobic organisms and the contents have an extremely foul odor. These are called putrid abscesses. Those without anaerobic infection are called nonputrid.

**Etiology**—(1) Pulmonary cysts which become infected by the hematogenous or bronchial route present a condition clinically identical with other lung abscesses, except in being slightly more difficult to treat. Rigler<sup>24</sup> has described this process in detail. He recommends *complete extirpation* of the cyst without drainage except in very severe cases.

(2) Infarcts of the lung (embolic) from septic foci elsewhere. They are often multiple and contain the same organism as the original septic site. Moore<sup>52</sup> believes most cases are of embolic origin.

(3) Aseptic infarcts of the lung such as seen in cardiac disease, becoming infected by the bronchial route. Chester and Krause<sup>49</sup> have re-

ported 18 cases following sterile pulmonary infarcts. In each case the infection was anaerobic in type. They have described the experimental superimposition of infection by the bronchial route upon infarcts.

(4) Foreign bodies in the lung substance. King<sup>15</sup> has reported its development in four of ten observed cases. They usually will not recover until the foreign body is removed and represent one of the urgent indications for surgery in these cases.

(5) Hematoma of the lung becoming secondarily infected. No doubt this process is similar to the infection of an aseptic infarct of the lung. Edwards<sup>13</sup> has reported this condition to be a relatively rare complication of hematoma of the lung. He also notes that there is a strong tendency for spontaneous cure.

(6) Necrosis of consolidated infected lung as in severe pneumonic processes.

(7) Infection occurring in the atelectatic segment of lung tissue distal to an obstruction of its bronchus. This is generally considered to be the commonest cause of clinical pulmonary abscess. The obstruction may be a neoplasm, benign or malignant; a foreign body of large size (such as a pencil eraser) or one of small size (such as a bit of tartar from teeth); a stenosis from cicatricial tissue; granulation in the lumen of a bronchus, or even a mucus plug. The commonest cause is aspirated infected foreign particulate matter, such as vomitus, tartar from teeth, or a bit of blood clot.

The bacteriology of lung abscess varies with its etiology. Most putrid abscesses contain the anaerobic or microaerophilic streptococcus and the fusospirochetal combination of Vincent's disease. Any other organisms may be found mixed with these. The nonputrid abscesses are more likely to contain pure cultures of a single strain of organism, such as staphylococcus, pneumococcus, Friedlander's bacillus.

**Pathogenesis**—Since that of those based upon infarction, hematoma, foreign body in the lung, pneumonia, etc., is rather obvious we need only consider that due to bronchial obstruction plus infection. An aspirated foreign particle is aspirated into the smallest bronchus or bronchiole into which it will fit, com-

monly one less than one-eighth of an inch in diameter. The bronchial mucosa becomes irritated and swells, completely blocking any further passage of air past this point. The air which is in the bronchopulmonary segment distal to the blockage is rapidly absorbed, causing an atelectasis of that segment. If no organisms are present in the segment or on the foreign body, the atelectasis remains uncomplicated by infection and the only symptoms are those due to mechanical changes from shrinkage of the lung segment and compensatory mediastinal shift. But if organisms are present in the segment, or are introduced with the foreign body, infection is set up in the atelectatic lung tissue. If the blockage persists, suppurative pneumonitis and later necrosis of the segment takes place. The shape of the bronchopulmonary segment is approximately that of a cone (wedge-shaped to the x-ray film) with the apex at the bronchus and the base on the visceral pleura. The necrotic process extends to the visceral pleura and through it unless localizing adhesions have occurred between it and the adjacent chest wall, mediastinum, diaphragm, or lobe (according to location). There are usually dense adhesions formed early in the process, and it is these which permit the performance of a one-stage drainage without pleural contamination, in most cases. The necrotic process also extends to the apex of the segment, and eventually past the obstructed part of the bronchus. The liquefied central portion of the segment can then drain into the tracheobronchial tree, and air can enter the cavity. At this point the patient suddenly expectorates considerable, usually very foul smelling, sputum, and x-ray will then reveal a cavity usually with a fluid level. If bronchial drainage is dependent and adequate, the fluid level disappears and the sputum becomes nonfoul,

then less purulent, then less in amount. Serial x-rays then show a rapid diminution in the size of the cavity to the point of complete disappearance except for a small fibrotic scar. When bronchial drainage is inadequate, the fluid level remains, the cavity does not shrink appreciably, and the sputum remains foul and large in quantity. At any time there may be a sudden flare-up with spreading pneumonitis in the affected lung, and subsequently other cavities may appear in this pneumonitic portion. Gradually the wall of the cavity becomes thick and fibrous, and chronicity sets in. At any time sudden pulmonary hemorrhage may appear. It is usually not fatal but may be. Metastatic abscesses to other parts of the body, especially to the brain, may appear either in the acute or chronic stages. If pleural adhesions are not formed early or adequately, sudden perforation into the pleura may occur. The lung suddenly collapses nearly completely, shutting off further bronchial drainage. A positive pleural pressure develops, causing an extreme mediastinal shift to the opposite side. If the patient survives the initial severe accident, he develops a large virulent empyema of the pleural space, complicated by a bronchial fistula. This condition is truly a surgical emergency.

**Symptoms**—Following a pulmonary infection, recognized or unrecognized, or a history of aspiration of vomitus, or a tooth or tonsil extraction by about two weeks, the patient who has been troubled by slight fever and a hacking nonproductive cough notices a sharp pleuritic pain in his chest. This is due to the formation of visceroparietal adhesions. Fever with or without chills increases. Remember that the severity of the symptomatology depends upon the size of the segment involved and virulence of the organism. The whole course may resemble a clinical pneumonia with high fever,

toxemia, cyanosis, and dyspnea, or it may seem to be just a mild influenzal attack.

Suddenly in another seven to ten days the patient begins to have profuse expectoration of purulent, perhaps blood-tinged material, usually of a very foul odor.

**Diagnosis**—The clinical history, the foul sputum (when present), the finding of the cavity on the x-ray film with or without a fluid level, and the absence of tubercle bacilli and presence of organisms in the sputum compatible with lung abscess point definitely to the true diagnosis. Bronchoscopy should always be done for diagnosis, at least. The presence or absence of a foreign body, tumor, or stenosis of the bronchus can thus be determined.

**Prognosis**—Under inactive (so-called conservative) management about 50 per cent die within 18 months, 25 per cent recover, and 25 per cent become chronic pulmonary invalids.

**Treatment — Prophylaxis** is often possible, and is certainly preferable. Children should be watched and trained not to put foreign bodies in their mouths. Patients should be instructed not to neglect their teeth and gums, and have regular dental attention. The dentist and rhinolaryngologist should be persuaded not to lose bits of teeth or tissue into the air passages. Greater care is necessary in preventing aspiration of vomitus after anesthesia, or other unconscious states, such as coma, alcoholism, drug poisoning, etc.

Prompt **bronchoscopy** after the inhalation of foreign bodies, and in the treatment of atelectasis, postoperative or otherwise, will prevent the development of pneumonitis and abscess. Schmidt, Mousel, and Harrington<sup>50</sup> have stressed that bronchoscopy be done for atelectasis

within 48 hours of aspiration or operation, as after 72 hours some degree of pneumonitis is usually present. Moersch<sup>51</sup> agrees with this but advises that in all anesthetic cases where secretion is present in the airways, tracheal aspiration be done before leaving the operating table by passing a suction tube between the vocal cords. Both groups stress the frequency of atelectasis postoperatively in upper abdominal and thoracic operations. If the obstruction is relieved early, no suppuration will occur, even though infective organisms are present. It takes both obstruction and infection to produce a suppurative pneumonitis. And even in fully developed abscesses, removal of a foreign body, or obstructing tumor (adenoma), or obstructing bronchial granulations will often effect a prompt cure. **Repeated bronchoscopy** for the purpose of aspirating the secretions and facilitating drainage is less sound. Usually if the bronchial orifice is sufficiently large for adequate drainage, the patient will recover promptly after any gross obstruction is relieved by the first or second bronchoscopy. If the bronchus is too small for adequate drainage, it is too small for the bronchoscopic aspirator to pass and it cannot be dilated. If the bronchial orifice is tamponaded by blood or fibrin clot, or pieces of slough too large to leave the cavity, no type of bronchoscopic treatment is able to relieve the condition. If rapid improvement does not follow the first treatments, as shown by loss of foul odor of sputum, diminution in symptoms, amount of sputum, size of cavity on x-ray, and disappearance of the fluid level on x-ray, so that there is no reasonable doubt that the patient is rapidly recovering, bronchoscopic treatments should be abandoned and **surgical measures** instituted. Remember that at any time a severe hemorrhage, brain abscess, or spreading pneu-

monitis may make the patient inoperable, and also that every week makes the condition more chronic. Chronic cases require extensive surgery for cure, while most acute ones require only simple drainage.

Medical management of these cases includes *postural drainage*, in whatever position experiment shows best for ease and completeness of expectoration, *transfusions, infusions, oxygen therapy, iron, arsenic, expectorants*, and *sulfonamide* therapy. Recently, *penicillin* has been available for a very limited number of cases. Its effects have been most impressive and to the author's observation have been responsible for saving a couple of otherwise lost cases. It should probably be given early in the stage of pneumonitis rather than later. When sufficient destruction of lung tissue, bronchiectasis, and chronicity have developed, even though toxicity can be removed and the general condition improved, the organic changes still require pulmonary resection, and relapse may be expected as soon as the penicillin is discontinued, if adequate surgery is not performed.

*Phrenic paralysis* has been tried at times in these cases in an attempt to obliterate the cavity. Since the diaphragmatic function is necessary for effective coughing, this measure interferes with drainage and should be condemned.

*Thoracoplasty* is extremely dangerous in acute cases but may sometimes be successfully employed in old well-drained chronic abscesses to obliterate the cavity. It is very destructive to the chest wall and pulmonary function.

*Pneumothorax therapy* with its separation of the pleural surfaces, perhaps before adequate walling off about the abscess has occurred, and its tendency to diminish the bronchial lumina or even kink them is a dangerous treatment.

However, Tewksbury and Fenton<sup>52</sup> have suggested that the failures were due to the institution of too much pneumothorax collapse. They advise a *marginal pneumothorax* so that no interference with bronchial drainage will result, and permit merely a selective shrinking of the cavitary area until its walls approximate and heal. They report a series of 45 cases so treated over a period of 25 years. Thirty-five recovered, four died. The idea is enticing and their results are excellent, but it is not likely that many others would have the patience and skill necessary to duplicate these results.

*Surgical drainage* of acute abscess would seem to be the logical, and has come to be the generally accepted, treatment in most cases. Moore<sup>53</sup> and Neuhof and Hurwitt<sup>54</sup> have recently discussed this treatment. The latter have reported 160 cases so treated with only four deaths. They maintain that pleural adhesions occur and are adequate very early, and that the one-stage operation may always be done if accurate localization of the adhesions is attained. They recommend that *methylene blue* and *lipiodol* be injected under fluoroscopic guidance into the intercostal space just over the abscess. Then PA and lateral x-rays are taken to determine definitely the relationship of the spot of lipiodol to the center of the cavity. Then the rib is resected which is most nearly over the center of the cavity, as shown by the relationship of the blue oil spot to it. The cavity should be right under the periosteum of the resected rib. If more than one-quarter inch of compressed lung tissue must be traversed before entering the cavity, localization has not been accurate. They recommend complete unroofing of the cavity and opening of any loculations. If the pleura should be inadvertently opened during the unroofing, it should

be immediately closed by suturing and rarely will pleural infection ensue!

Neuhof and Touroff<sup>55</sup> discuss a "hyperacute" variety of acute putrid abscess characterized by a fulminating clinical course, short history, profound toxemia, with a large excavation often with an scalloped border and a high fluid level, and extensive pleural reaction. Most surgeons have avoided surgery in these cases but they strongly recommend very early *surgical drainage*. They report 38 cases with three deaths.

Other surgeons recommend the *two-stage drainage* of lung abscess. After localization, the ribs overlying the abscess are resected and the wound is then packed. Some men recommend a fairly extensive extrapleural freeing of the lung about the area and packing of this extrapleural space. After seven to 14 days it is considered that the visceral and parietal pleura must be very adherent and the second stage is done. The abscess, located by aspirating the lung, is widely opened and packed, preferably with *activated zinc peroxide suspension on plain gauze*. In those cases where extrapleural stripping is done, the cavity often perforates spontaneously between the stages, since the outer cavity wall is relatively avascular.

It would seem that the two-stage drainage is safer when in doubt about the adequacy of pleural adhesions or the accuracy of localization. The one-stage method establishes drainage earlier, and flare-ups between the stages are thereby avoided.

In acute moderate sized abscesses, the cavity rapidly shrinks after proper external drainage and the walls soon become lined with granulations which eventually obliterate the cavity completely, provided adequate and *prolonged* drainage is maintained. If the cavity is very

large or the case is much over six weeks' duration before surgery, the walls become epithelialized with drainage and we then have a bronchocavitary-cutaneous tract of variable size. If the external wound is permitted to heal in, closing the skin over the cavity, we then have an epithelialized cyst-like cavity with bronchial communication. This may remain clean and symptomless if the bronchial drainage is adequate. But if the bronchial openings are small or become so during the course of a respiratory infection, then a return of suppuration may be expected. It is therefore preferable that, once epithelialization has appeared, a plastic operation be performed in which a pedicled muscle flap is sutured into the cavity to obliterate both its lumen and the bronchial openings.

In cases with multiple cavities located in one lobe (or one lung), it is advisable that early *lobectomy* (or *pneumonectomy*) be done because poor results are obtained by multiple drainage operations.

Chronicity, very large cavities, and associated bronchiectasis also require *pulmonary resection* for complete cure.

### Bronchiectasis

Bronchiectasis may be either congenital or acquired. Congenital cystic disease of the lungs, congenital cystic bronchiectasis, and cases with congenitally large bronchial tubes are closely related. If these conditions are not associated with infection they usually have no surgical significance. Likewise, acquired enlargement of part of the bronchial tree has no surgical significance unless "it is associated with persistence of infection." We are therefore only interested in patients with dilatations of part of the bronchial tree plus suppurative (often anerobic) infection—"suppurative bronchiectasis."

Clinical suppurative bronchiectasis is classified as cylindrical (or fusiform),

saccular, and mixed in type, and also as dry and wet. The cylindrical form is one in which there is generalized enlargement of the diameters of the bronchial branches in the affected region. These dilated bronchi, although their cilia are usually destroyed, have good drainage and, therefore, infection is less prominent than in the other types. These cases tend to be "dry," that is, to have little purulent sputum. They have a greater tendency to hemoptysis than the saccular type and this at times may be very severe. The saccular type is one in which there are saccular dilatations in the affected part of the bronchial tree. There are often stenoses or kinks proximal to the sacculations which greatly interfere with drainage. Hence, infection is more prominent here, with a tendency to "wetness," that is, a profuse mucopurulent sputum. Most cases have both cylindrical and saccular types of dilatations (mixed). Most cases have a tendency to alternate between wet periods with much purulent sputum and signs of sepsis, and dry periods with remission or absence of symptoms.

**Etiology** — The cause of congenital suppurative bronchiectasis is cystic bronchiectasis upon which is superimposed infection. The acquired type is due to bronchial obstruction plus infection. Tannenbergh and Pinner<sup>56</sup> seem to have proved this very well experimentally. They have shown that: (a) Complete atelectasis of lung tissue due to bronchial obstruction in the absence of infection may be present for months without producing any permanent lung changes; (b) ligation of the pulmonary artery does cause fibrosis but no bronchiectasis distally; (c) high negative intrapleural pressure has no effect upon the diameter of normal bronchi; (d) infection in a bronchopulmonary segment plus obstruction

of its bronchus routinely produces typical bronchial dilatations within three to four weeks; (e) infection of the segment in the absence of bronchial obstruction does not produce bronchial dilatations.

Kennedy<sup>57</sup> has shown that seven to 14 days after an ordinary "cold" there is usually a patch or two of increased density in the lung fields which disappears in most cases within two weeks. He believes this is probably an area of atelectasis or deficient aeration of a pulmonary segment. Brennemann<sup>58</sup> states that: "according to prevailing evidence, bronchiectasis, at least in children, is nearly always, perhaps always, preceded by atelectasis." He feels that this atelectasis is often due to complete obstruction of a bronchial lumen by a mucous plug. It frequently follows pneumonias and other respiratory infections of children, including sinusitis. Fibrosis occurs and causes emphysema of the air cells close to the infected areas. These then become emphysematous cyst-like spaces which are responsible for the honeycombed appearance seen on the x-ray film rather than the dilatations of the bronchi, as previously thought.

Lederer<sup>59</sup> has shown that sinus disease in children is commoner than previously believed. Shortly after a sinusitis the bronchial mucosa becomes inflamed. He suggests that the rôle of allergy may be important in this relationship. At any rate, secretions from the infected sinuses may readily enter the tracheobronchial tree and set up infection and swelling of the mucosa.

Wishart<sup>60</sup> found sinusitis present in 84 of 433 children with bronchiectasis (19 per cent). In 15 cases there was a definite history of inhalation of a foreign body. He states that the "bacteriology of bronchiectasis is the bacteriology of

the bronchopneumonia or acute respiratory diseases which mark the onset of symptoms."

Clerf<sup>61</sup> believes that bronchiectasis is usually acquired and that it is due to bronchial obstruction plus infection. He stresses that bronchiectasis is commoner than tuberculosis. He advises early and repeated *bronchoscopy* in cases of atelectasis, especially those following pneumonias in children, to remove the tenacious obstructing mucous plugs.

Riggins<sup>62</sup> feels that sinus disease comes later in life than bronchiectasis and attributes the latter to repeated bronchopneumonias occurring in childhood.

Kent<sup>63</sup> reports 10 cases of childhood tuberculosis in which pressure from enlarged tracheobronchial lymph nodes produced atelectasis. Seven of these developed bronchiectasis in the atelectatic lobes.

Aufses<sup>64</sup> has shown the frequency with which bronchiectasis of the upper lobes follows tuberculous endobronchitis.

The development of bronchiectasis following bronchial obstruction by foreign body, neoplasm, or stenosis is well recognized.

In summarizing, it may be said that acquired bronchiectasis follows bronchial obstruction plus infection. In children it usually follows atelectasis of the lower lobes due to mucous plugs remaining after severe respiratory infection.

**Pathology**—The bronchi are dilated and there are various stages of destruction in the bronchial wall. The least is a loss of cilia and change in the epithelium to a squamous type. There is increase in the submucosal connective tissue. In more advanced cases the mucosa contains areas of ulceration and desquamation, and may be partly covered by crusts or slough. In farther advanced cases the mucosa is replaced by granulation tissue and, at least in the more distal

bronchi, the cartilages are destroyed and replaced by fibrous tissue. In the most advanced cases, and especially in large saccular dilatations, the wall of the sacculus is made up of compressed lung tissue and granulations.

**Symptoms**—The patient may date the onset of his trouble to an attack of bronchopneumonia following which he has had a persistent or recurring cough with mucopurulent sputum. There are often periods of remission in which the cough disappears. Then exacerbations occur with much cough and sputum, temperature, and perhaps hemoptysis. There may be recurrent attacks of "pneumonia," usually always in the same lobe.

Physical examination may reveal an area of dullness and bronchovesicular breathing in one of the bases, with moist râles. Clubbing of fingers and cyanosis is present in advanced cases.

**Diagnosis**—X-ray may reveal an area of definite atelectasis, or perhaps just increased bronchial markings, or perhaps a normal appearance of the chest. Anspach<sup>65</sup> has stressed that any "unresolved pneumonia" may represent atelectasis with or without bronchiectasis, especially when it occurs in children. He advises bronchography in all cases clinically or roentgenologically suspicious.

Bronchoscopy may reveal granulations and typical secretions, but they may occur in the absence of bronchiectasis. Clerf<sup>61</sup> points out the absence of abnormalities during the dry stages of bronchiectasis.

Bronchography is the measure which will accurately diagnose every case anatomically, and if the clinical history fits, the diagnosis is made. Dormer, Friedlander, and Gibson<sup>66</sup> have carefully considered the various methods of performing bronchography—oral, nasal, by intratracheal catheter, and bronchoscopic. They prefer the nasal method and report



its successful employment in 250 cases, using iodized poppy-seed oil. The important thing, if surgery is considered, is that all branches of the tracheobronchial tree are properly outlined. Then an exact knowledge of the extent and distribution of the disease permits exact surgical planning.

**Prognosis**—The changes in well developed suppurative bronchiectasis are irreversible and intermittently or steadily progressive. Cure cannot be obtained by anything but excision of the diseased lung tissue. Bradshaw and O'Neill<sup>89</sup> report a mortality of 35 per cent for untreated bronchiectasis over a ten-year period. The morbidity is very high but hard to estimate because of the prolonged period of remissions and exacerbations. Suffice it to say that these people are chronic pulmonary invalids.

**Treatment — Prevention** again is most important when practicable. The etiology of aspiratory lung abscess and acquired bronchiectasis are similar except that in the latter the bronchial obstruction is not so complete, or is intermittent, or the virulence of the bacteria concerned is less, or some combination. Therefore, again we may try to prevent aspiration of foreign bodies by children, of vomitus by the unconscious, etc. If atelectasis does occur postoperatively or postpneumonically, it should be treated promptly and vigorously by **bronchoscopic aspirations**. Especial care should be given to sinusitis in children. All cases of severe bronchitis or pneumonia, especially in children, should be followed by serial x-rays. Any suggestion of patchy atelectasis or slow resolution should be investigated by bronchoscopy and bronchography.

Once a fully developed suppurative bronchiectasis is completely diagnosed by bronchography, consideration of **resec-**

**tion therapy** is in order, since that is the only hope of complete cure. Kent and Blades<sup>67</sup> have described the anatomy of the pulmonary lobes with the commoner bronchial and vascular abnormalities. Intimate familiarity with these structures is necessary if complete yet conservative resection of the diseased segments is to be achieved. Remember, the disease is not necessarily distributed to a complete lobe or lobes, but occurs in bronchopulmonary segments of the various lobes. Therefore, we may find a patch of bronchiectasis in one of the basal divisions of the left lower lobe and another patch in the lingular division of the left upper lobe. It would be futile and destructive of lung tissue to remove the entire lower lobe and leave the entire upper lobe intact. DeBakey and Ochsner<sup>68</sup> and Blades<sup>69</sup> have both stressed the importance of careful delineation of the diseased segments preoperatively by bronchography, and operatively by finding rudimentary fissures, by occlusion atelectasis, and by differential inflation of the various segments.

Bradshaw and O'Neill<sup>89</sup> report a mortality of four per cent in operations for minimal bronchiectasis. In cases requiring **extensive bilateral surgery**, a mortality of 44 per cent was obtained.

Johnson<sup>39</sup> advises that in all cases of **total pneumonectomy** for bronchiectasis, a **thoracoplasty** should be done to obliterate the space and prevent destructive emphysema from occurring in the good lung.

Gowar<sup>70</sup> has strongly recommended that pleural adherence be produced on the operative side at some time prior to the performance of **lobectomy** for bronchiectasis. When a lobectomy is performed in the presence of a free pleural space, the possibility of a total empyema is a real one. Unless the remaining lobe

can be rapidly reexpanded partly to fill the space, empyema, should it develop, would necessarily have to be a total one. Now if thick infected mucopus should be inadvertently milked into the good lobe during the operative procedure and suffice to occlude its bronchus, it would not be possible to reexpand that lobe postoperatively. This lobe would then become completely atelectatic, and soon become the site of a suppurative pneumonitis, perhaps of multiple abscesses. To avoid these very serious complications, Gower advises using one-half per cent *iodized talc* introduced one to two months preoperatively through a powder blower.

To date, the most *extensive bilateral pulmonary resections* done have comprised removal of the left lower lobe and lingular division of the left upper lobe, and the right lower and middle lobes. Needless to say, bilateral surgery is not done all at the same operation. It would seem likely that no more extensive procedures than the foregoing will ever be feasible. However, these patients seem to do very well after recovery and have very little dyspnea, except on severe exertion.

For those who cannot be benefited by surgery, we can offer a few things. *Postural drainage* is often helpful if carried out indefinitely. *Palliative bronchoscopy* is of great benefit and many persons continue under this treatment for years. If the patient is better in the summer and worse in the winter, it is worth-while to send him to a *warm, dry climate*. Some persons then improve enough to live nearly normal lives, but they must never plan to return to the cooler climate. *Autogenous vaccines* made from the bronchoscopic aspirations are sometimes of help. Davison<sup>71</sup> stresses the importance of allergy in bronchiecta-

sis and advises *desensitization measures*.

Once the bronchiectatic process is completely extirpated, the patient becomes practically normal unless his vital capacity is too greatly impaired. Many persons are able to do hard, laborious work after total pneumonectomy. The life expectancy in these persons becomes normal after removal of the source of recurrent infection, unless the vital capacity has been reduced to the point where a simple bronchitis would endanger life by slightly diminishing it.

### Bronchial Asthma

Bronchial asthma is, in its more severe forms, a troublesome, incapacitating disease. If it is persistent or frequent in recurrence, it leads inevitably to the development of pulmonary emphysema and myocardial deterioration. Sudden death during the attacks is not as rare as commonly believed.

Some cases are easily recognized as being due to a specific allergy and are easily managed by desensitization or removal therapy. Other cases are easily managed by general medical and hygienic measures. Some are bacterial in origin and can be helped or cured by the treatment of sinuses, teeth, tonsils, etc., or perhaps helped by vaccine. Their remains a fairly large percentage of severe asthmatics who are not helped by the usual measures. Miscall and Rovenstine<sup>110</sup> believe that in some types of asthma the breathing is a response to exaggerated reflex activity carried by the pathways over which the normal reflexes usually flow. The stimulus originates in the lung and the afferent pathway is over the sympathetic nervous system. The efferent pathway is over the vagus nerve. Destruction of the stellate, second, third, and fourth dorsal sympathetic ganglia interrupts the af-

ferent pathway. It is recommended that a test alcohol block be carried out upon these ganglia on the right. If relief is thus obtained, later surgical *sympathectomy* of this portion of the chain is indicated. In 61 patients treated by these authors, 78 per cent were immediately improved; 21 of these were later operated upon and all were relieved of their asthma.

### Pulmonary Tuberculosis

The diagnosis of pulmonary tuberculosis is being accomplished earlier and more efficiently than ever before. Yet there is still a grave tendency among many physicians to rely upon the development of definite physical signs and typical symptoms before advising x-ray examination. Our foremost phthisiologists find themselves badly handicapped or even helpless in diagnosing chest conditions without adequate x-rays and sputum studies. To this might be added bronchoscopy and bronchography (installation of iodized oil) in many cases. It is not our intention to decry the exhibition of careful history taking and physical examination, but merely to point out that a reasonably accurate diagnosis of chest conditions can no more be attained by these means than it can in many other serious conditions, such as syphilis and diabetes. We heartily endorse the recommendation that all hospital admissions be followed by a routine chest x-ray just as they are by a Wassermann test and a urinalysis.

**Diagnosis**—Diagnosis is usually readily established by: (a) Index of suspicion; (b) x-ray of chest, and (c) finding of tubercle bacilli in the sputum.

**Treatment**—We have nothing generally more specific than *rest*. The usual indication for *surgery* (including *pneumothorax*) today is the presence of pulmonary cavitation.

In the treatment of pulmonary tuberculosis, *collapse therapy* is being employed ever more extensively, but more selectively than before. The *phrenic nerve operations* are somewhat less frequently used, and then more commonly in association with some other measure, such as *pneumoperitoneum* or *pneumothorax*. Permanent forms of phrenic interruption have been largely abandoned, at least until after a previous performance of a temporary test interruption. Ellison and Tittle<sup>78</sup> have shown the much greater effectiveness of phrenic paralysis in closing right apical cavities than those on the left.

Greenfield and Curtis<sup>72</sup> have estimated that complete phrenic paralysis diminishes the volume of the affected lung by one-sixth to one-third. They stress the importance of the "sniff" test in proving the presence of diaphragmatic paralysis. The patient is told to "sniff" in strongly while being fluoroscoped. If the phrenic nerve has really been paralyzed, the corresponding hemidiaphragm will move upward (paradoxically) while that on the intact side moves downward.

*Artificial pneumothorax* is more widely used, particularly in early lesions, but is avoided in many conditions where previously employed. In any case where endobronchial ulceration or stenosis is associated, pneumothorax therapy is likely to cause serious complications, such as atelectasis, empyema, secondary sepsis from bronchial obstruction, and unexpandable lung. Packard and Davison recommend *bronchoscopic treatment* to heal the ulcerations before induction of pneumothorax. Clerf<sup>73</sup> classifies tuberculous tracheobronchitis as: Infiltrative lesions, the granulomatous, the ulcerative, and the fibrostenotic ones. These latter represent the healing stage, and reduce the size of the bronchial lumen.

This is not necessarily serious unless there is retention of secretions distal to the stenosis.

Benedict<sup>74</sup> has described the various lesions and symptomatology in detail. He recommends diagnostic bronchoscopy in any case of tuberculosis presenting atelectasis, wheezing, difficulty in raising sputum, intermittent and persistent cough, unexplained febrile attacks, or positive sputum in the absence of parenchymal disease.

Rafferty and Shields<sup>75</sup> note that the prognosis in pulmonary tuberculosis with tuberculous tracheobronchitis depends more upon the latter than upon the parenchymal disease. They feel that pneumothorax therapy should not be employed except with very slight ulcerative or infiltrative lesions of the bronchus. They prefer thoracoplasty in these cases.

Pneumothorax is being employed less frequently in cases with extensive lung destruction where a good collapse is usually not easily obtainable because of adhesions, and even if produced, usually leads to a permanently unexpandable lung. In any case where a good collapse cannot be obtained, it is dangerous to continue pneumothorax therapy, as there is likelihood of contralateral spread, empyema, bronchopleural fistula, fibrosis of the collapsed lung, and unexpandable lung if persisted in. Probably three months should be the extreme limit of maintaining an ineffective pneumothorax unless there is good reason to believe that cavity closure and sputum conversion are imminent. This reasoning implies that necessary section of adhesions must be undertaken soon after the initiation of the collapse. Then if thoracoscopy reveals that collapse cannot be improved by this means, the pneumothorax should be promptly abandoned so that precious time will not be lost, and so

that other effective measures may be instituted.

Goorwitch,<sup>76</sup> in reviewing 73 cases of thoracoscopy without pneumonolysis, was able to find no complication from this operation except transient postoperative fever. Postoperative pleural effusions were present in 17 per cent but some which were already present became promptly absorbed. Actually effusions had been present preoperatively in 20 per cent. This study is most interesting because it does away with much of our previous fear of complications from thoracoscopy in tuberculous cases. Apparently one need not hesitate to look in a thorax in which there is serious doubt that any adequate pneumonolysis can be performed.

Pneumoperitoneum is a method of pulmonary collapse brought about by instilling air or nitrogen into the peritoneal cavity. This is maintained by repeated air refills at pressures higher than atmospheric. Its effect upon the lung is brought about by raising the diaphragm, thereby lessening the apicobasal diameter of both lungs. It causes a general bilateral lung relaxation which helps the diseased lung tissue to retract and fibrose. Actual cavity closure can be obtained not infrequently by this measure. It must be remembered that the elevation of the diaphragm is associated with arching and stretching of its fibers. This causes greater diaphragmatic respiratory excursions, which often improve respiratory function, particularly in emphysematous persons. Also the greater excursions increase the effectiveness of coughing, enabling patients to eliminate thick mucus more easily—a great aid in many cases with associated bronchiectasis, and particularly those with basal lesions. When a more extensive unilateral effect is desired, a *phrenic*

*nerve interruption* is combined with the *pneumoperitoneum*. In these cases a very high unilateral diaphragmatic rise is obtained.

*Extrapleural pneumothorax* is a method of obtaining pulmonary collapse comparable to a pneumothorax where a free pleural space does not exist. A great dead space is produced by stripping the parietal pleura away from the chest wall, the cleavage taking place in the layer of the endothoracic fascia. This space is then maintained by air refills similar to an intrapleural pneumothorax.

Karlen<sup>77</sup> has made a very complete anatomicosurgical study of the endothoracic fascia. He reports that cleavage of this fascia is possible at all points except over the dome of the diaphragm and the pericardium (except in the region of the phrenic nerves and the fatty pads).

Alarcon<sup>79</sup> still believes extrapleural pneumothorax to be preferable to *thoracoplasty* in most cases.

However, Russo<sup>80</sup> and Geary<sup>81</sup> advise against it after a comparable experience, except under special conditions, such as in children, in hemorrhage, and in certain very poor risk cases.

Extrapleural pneumothorax has been largely abandoned, for several reasons, notably the danger of infection of the large created dead space, the likelihood of cavities perforating into the space, and the problem of eliminating the space after the healing is complete and the lung has become unexpandable. It is occasionally of great value in certain individual cases where a quick extensive collapse is necessary. Here the case should usually be completed by later conversion to *thoracoplasty* except in growing children, where the progressive extreme deformity from thoracoplasty is prohibitive.

*Thoracoplasty* has come to be more standardized in recent years and much more effective in properly selected cases.

It should usually be limited to unilateral cavitary cases in which the disease has become stabilized and is not actively progressing and preferably limited to the upper lung field. Unstable, rapidly progressing lesions do not usually respond well to this treatment. Lower lobe cavities, hilar lung cavities, and giant cavities do poorly with thoracoplasty. Cavities which have a check-valve mechanism due to a partially blocked draining bronchus remain expanded under any form of collapse therapy due to their high intracavitary pressure. Therefore, we attempt to avoid thoracoplasty in all of these situations, although certain associated features of any case may necessitate its performance.

The routine use of apicolysis (extrapleural freeing of the lung apex) in the first stage of thoracoplasty is much less common in present-day thoracic surgical clinics. Its employment is associated with an increased incidence of wound infection, paradoxical breathing, and operative shock.

Also in some cases depression of the lung apex causes a drop of the cavity to a much lower level in the lung field, necessitating resection of more ribs to produce collapse of the diseased area. Of course, where a total thoracoplasty is planned, the additional apicobasal collapse may be desirable.

Modern thoracic surgical clinics practically invariably start the thoracoplasty at the top and include removal of the first rib. The classical curved paravertebral incision starting about at the level of the second dorsal spinous process, running down midway between spine and vertebral border of the scapula, and sweeping around below the inferior scapular angle nearly to the posterior axillary line is the most popular incision. Long lengths of two or three ribs are removed at each stage. Subsequent stages are

made through the same incision. The modern tendency is to take greater lengths of fewer ribs at each stage. This may increase the number of stages but markedly diminishes the postoperative disturbance to the patient, especially paradoxical breathing. Eventually an excellent anatomical collapse is obtained. Some clinics routinely remove the vertebral transverse processes with the ribs. This increases the collapse but also increases the tendency to postoperative scoliosis, particularly if the erector spinae muscles are injured.

Recently certain of the more advanced clinics have adopted a routine or nearly routine *anterior thoracoplasty* stage to complete the decostaliation. This measure should prevent the persistence of positive sputum in those cases with anterior cavities, or extensive cavitation, part of which extends anteriorly.

At least two thoracic surgical clinics in Philadelphia have recently adopted the *multiple small stage muscle-splitting thoracoplasty procedure* described by Jerome Head several years ago as their routine thoracoplastic operations. Here, through small anterior and posterior incisions which split the chest wall muscles on the gridiron principle, half lengths of three or four ribs are removed at each operative stage. Operative hemorrhage and shock are negligible, and the postoperative course is usually very smooth. This is of particular value during the present shortage of nurses. It is interesting to note that Holman<sup>82</sup> is recommending the use of two small longitudinal incisions at one stage, one posteriorly and one anteriorly, to permit complete decostaliation of the upper ribs and to avoid trauma and some muscle destruction. At a later stage he makes another small posterior incision and removes part lengths of the next few ribs. It would

seem that the muscle splitting incisions would have all the advantages Holman mentions, and besides would be designed to avoid entirely any muscle destruction. Modern thoracoplasty produces cavity closure and conversion of sputum in 70 to 75 per cent of cases with a mortality of about seven per cent.

Harrison and Berry,<sup>83</sup> in a recent review of 150 cases of classical thoracoplasty, found that 74.7 per cent of their 107 cases of parenchymal disease had become sputum negative and apparently arrested; 4.7 per cent had died, probably from the surgery. Of 38 cases of tuberculous empyema (various types), 63.2 per cent were cured and 7.8 per cent had died.

*"Monaldi" drainage* of tuberculous cavities is employed especially in cases of "check-valve" cavities where the intracavitary pressure is above one atmosphere. It is sometimes used as a palliative drainage operation for ordinary giant cavities. After adequate assurance that the lung is adherent over the area of cavitation, a trocar and cannula are inserted through the chest wall into the cavity. Either a rubber or metal catheter is then placed in the cavity and continuous suction of 10 to 20 cm. water is applied for months. The cavitory drainage lessens, becomes mucoid, and finally sterile to tubercle bacilli. The cavity rapidly shrinks, and in check-valve cases becomes merely a sinus tract about the catheter. Unfortunately, when the catheter is withdrawn the cavity usually reopens and its secretions soon become positive for tubercle bacilli. In 20 to 30 per cent of cases the cavity does not reopen. Recently the tendency has been to use Monaldi drainage in conjunction with thoracoplasty or as a palliative measure. It is interesting to read Elliott's<sup>84</sup> account of Hastings using cathe-

ter drainage of tuberculous cavities in 1845.

**Open drainage** of cavities by simple unroofing after insuring pleural adhesions has been reported by Rogers, Shipman, and Daniels.<sup>85</sup> Of 11 cases so treated eight had sputum conversion and complete healing of the wound. The early results are encouraging, but the danger of extensive tuberculous infection of the chest wall is such that this measure will probably never have any great popularity.

**Pulmonary resection** for tuberculosis has been done intermittently since 1891 by Tuffier and other daring surgeons. There have more recently been many cases resected under a mistaken diagnosis of bronchiectasis or lung tumor. In general, the results have been most discouraging, with occasional brilliant recoveries. Recently, however, after due consideration of the special problems, a specialized technic has been worked out by some leading thoracic surgeons, which has led to consistent and satisfactory results. Behrend<sup>86</sup> has recently reported a successful case of *pneumonectomy* for pulmonary tuberculosis complicated by bronchostenosis. He feels that pneumonectomy is preferable to *lobectomy* because of the probability of involvement of the adjacent lobes. The recent report of six cases of lobectomy by Churchill and Klopstock,<sup>87</sup> and a series of 63 including both lobectomies and pneumonectomies yet to be published by Overholt,<sup>88</sup> leave little to be desired in operations of this magnitude for particularly bad cases. It would seem that those troublesome cases of unilateral acute pneumonic phthisis, lower lobe cavitation, hilar cavities, giant cavities, check-valve cavities, thoracoplasty failures, and cases with bronchostenosis will at last be largely amenable to surgical intervention.

Of Overholt's series, 35 were cases subjected to total pneumonectomy: 11 right-sided, 24 left-sided; 28 cases were subjected to lobectomy, five of which were for lower lobe disease and three were for middle and lower lobe disease. He estimated his statistics upon the last 45 cases, which were operated upon during the past two years by a modern technic. Thirty-six were reasonable risks and two died; nine were desperate risks and three of them died. He does not hesitate to divide a bronchus through an area of tuberculous endobronchitis and has noted no particular difficulty with healing. Pleural effusion positive for tubercle bacilli is apparently no contraindication to resection. Acute exudative processes which are so dangerous when subjected to collapse therapy present no particular problems in resection surgery. Contralateral disease is no contraindication unless it is itself a fatal type of process.

### Tuberculous Empyema

**Definition**—Collection of pus in the pleura containing tubercle bacilli.

Tuberculous empyema is sometimes spontaneous in onset, but commonly is directly a result of pneumothorax therapy, particularly of prolonged inefficient pneumothorax therapy. Therefore, the most important practicable method of *prophylaxis* is to abandon useless pneumothoraces quickly.

A simple "idiopathic" pleurisy is usually considered to be tuberculous but it rarely turns into an empyema with or without treatment, even though tubercle bacilli may be found. Likewise, in many clear effusions developing during pneumothorax therapy there is little tendency to empyema formation even though tubercle bacilli can be found in the fluid. However, some pleural effusions do gradually thicken up and become purulent. A tendency to cloudiness and rapid re-



accumulation of the fluid should make one seriously consider abandoning the pneumothorax to avoid the probably imminent empyema. Morriss<sup>104</sup> reports 7.1 per cent tuberculous empyema in 370 pneumothorax cases. One-half of these cases died.

Fully developed tuberculous empyemas may be considered as of four types: Simple tuberculous, mixed tuberculous (with secondary pyogenic organisms), and each of these with or without a bronchopleural fistula. Treatment for the simple tuberculous empyemas without bronchopleural fistula may be conservative, embracing *aspirations, irrigations, oleothorax*, etc. Probably the most satisfactory solution is *thoracoplasty with aspiration of the pleural fluid* before and after each stage.

The other three types of empyema are best handled by closed *thoracotomy* with or without irrigation, followed by *thoracoplasty*. There is usually a small residual empyema space left after thoracoplasty which requires a localized Schedé operation (removal of parietal pleura to completely unroof the empyema).

### Nontuberculous Empyema

**Definition**—An empyema is a collection of pus in the pleural space. It is usually caused by bacterial agents, but may be sterile. The presence of bacteria in a nonpurulent pleural effusion does not mean that an empyema is present; it only means that one is dealing with an infected pleural effusion.

Empyema may follow pneumonia, pneumonitis, or other pulmonary infectious process. It may occur from blood-borne infection. Pulmonary abscesses may rupture into the pleural space if pleural adhesions do not seal them off, and then commonly cause very severe empyemas. Traumatic chest injuries,

especially those associated with an open sucking wound or a badly lacerated lung, are prone to develop empyema. Thoracic surgery may be followed by empyema. The commonest organisms found are: Pneumococcus, staphylococcus, streptococcus, and the mixed type containing mouth organisms (fusiform bacillus, spirochete of Vincent, diphtheroids, anaerobic streptococci, influenza bacillus, etc.). The Friedlander bacillus, colon bacillus, *Bacillus pyocyaneus*, Welch bacillus, and *Bacillus proteus* are less common.

The precursor of infectious empyema is the infected pleural effusion. This is thin, serous, often blood-tinged. It should be treated either by multiple thoracentesis without air replacement (every day or every other day), or by closed water-seal intercostal catheter drainage (Fig. No. 2) until it becomes a true empyema, with thick pus. If a bronchopleural fistula is present, intercostal water-seal drainage is preferable, since it maintains an empty pleural space and this should avoid the danger of aspiration of pleural contents into the tracheobronchial tree.

Once a true empyema with thick pus has developed, wider drainage is necessary. The common use of oral *sulfonamides* in these cases often modifies the thickness of the exudate (lessens it), depresses the leukocyte count and the temperature elevation, thus rendering unreliable the former criteria for determining readiness of an empyema for surgery. Berman<sup>92</sup> advises *fluoroscopy* after partial aspiration of the empyematous fluid, with air replacement, in various positions (upright, Trendelenburg, and lateral with the affected side down—Reigler position) to determine the presence of mediastinal fixation. Once this fixation is certain, open *thoracostomy* by rib resection is safe. Of 167 cases so treated, Berman reports only five deaths—2.9 per

cent mortality. Williams<sup>93</sup> injects some lipiodol and some air after pleural aspiration. These mark the lower and upper limits, respectively, of the pleural cavity, and so he is always able to obtain completely dependent pleural drainage. He does not wait for complete mediastinal fixation, fearing the effects of chronic sepsis. He advises removal of a long portion of one rib and production of a large opening through this rib bed, to obtain free drainage. He leaves the wound open and uses no drainage tubes. He reports 39 cases with one death.

Alexander<sup>94</sup> advises *rib resection* when the aspirated pleural fluid shows a sediment of 75 to 90 per cent of pus after standing overnight. However, he attempts to maintain a tight water-seal drainage even with rib resection. He makes a hole in the bed of the resected rib just large enough to admit a large (thumbsized) drainage tube which is sutured in place. The wound is left unsutured. This drainage tube is connected to a water-seal bottle. By this means a negative intrapleural pressure to favor lung reexpansion can be maintained even though a large thoracostomy tube is used.

The presence of a bronchopleural fistula causes constant re-infection of the pleural space with organisms from the mouth and tracheobronchial tree. And it prevents the production of a negative intrathoracic pressure because air leaks from it into the pleural space. It may even cause a positive intrapleural pressure if the air leak is valvular.

However, with really adequate drainage of the pleural space, almost any acute pyogenic empyema will rapidly heal by lung reexpansion and pleural adherence, regardless of the presence or absence of bronchopleural fistula. It is most essential that the drainage tube be kept in place until the pleural cavity is entirely obliterated about it. Then the tube should

be shortened (not replaced by a smaller calibered tube) gradually, say, one-half inch per week until it comes entirely out. Edwards<sup>13</sup> stresses that too early removal of the drainage tube is responsible for most cases of chronic empyema and persistent sinuses.

During the healing of the empyema, its size should be measured weekly by filling it with saline with the patient in a position to bring the thoracostomy opening to the top of the space. When bronchial fistula is present, this is impossible, and the shrinkage of the space can only be followed by serial x-ray films, plain, or with lipiodol instilled into the drainage tube.

When reexpansion comes to a standstill before complete healing, the empyema may be called chronic. Causes of chronicity are: Inadequate or too short drainage, open thoracostomy in the stage of infected pleural effusion, foreign body, osteomyelitis of a rib, bronchial fistula, bronchial obstruction, underlying chronic lung abscess. Clagett and Shepard<sup>95</sup> advise institution of a *wider drainage and constant Dakinization* as the first measure in treating chronic cases. In some cases it may be advisable to resect two or more ribs, excise the periosteum and intercostal bundles, and suture the overlying skin to the pleura. This provides wide open drainage which will be permanent until the lung reexpands and seals the pleural opening. Allison<sup>96</sup> advises that after a fair trial of *wide open drainage* the pleural space be obliterated by performing an *extrapleural strip-page* of the very thick parietal pleura, and compression of this membrane tightly against the collapsed lung surface by packing. In some cases he first decorticates the lung. The extrapleural space is at first just as large as the now obliterated pleural space, but it has better nourishment to its wall and heals much

better. It rapidly shrinks, reexpanding the lung, and the patient is then rid of both spaces without appreciable thoracic deformity.

Other treatments of chronic empyema include *thoracoplasty* or one of its modifications, such as the Estlander or Schede procedure. In these latter, not only are the ribs removed over the empyema cavity, but also the parietal pleura, periosteum, and intercostal bundles. The wound is then usually packed open and made to granulate in and eventually epithelialize.

Of course, the cause of the chronicity must be considered and removed if possible (foreign bodies, osteomyelitis of a rib). Dorsey<sup>97</sup> advised *thoracoscopy* of chronic empyema spaces, especially if they are anteriorly located or extend into the mediastinum. Dermoid tumors not infrequently become infected and may be drained under the impression that they are empyemas.

Congenital pulmonary cysts may also simulate chronic empyema as may a large epithelialized pulmonary abscess cavity. In all these cases the wall of the cyst or cavity must be completely removed before healing can occur.

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## MEDIASTINAL TUMORS

A great variety of tumors, benign, malignant, inflammatory, and vascular, may appear in the mediastinum.

Hodgkin's disease frequently presents its first appearance in the mediastinum. It is usually associated with typical adenopathy elsewhere, especially in the cervical and axillary regions. It presents a nodular mass in the mediastinum, usually bilateral, and frequently presents pulmonary infiltration. Diagnosis is made by the biopsy of an associated superficial gland or by the rapid disappearance of the lesions on the therapeutic test of the

roentgen ray. *X-ray therapy* is of great palliative value. Smith and Shefts<sup>98</sup> have reported a case with involvement of the left main bronchus causing obstruction and atelectasis simulating a bronchoepithelioma.

Lymphoblastomas, such as lymphosarcoma, leukosarcoma, mediastinal leukemia, and reticulum-cell sarcoma, are not uncommon in the mediastinum. They tend to present a more symmetrical oval or rounded mediastinal shadow. They may cause clear or bloody pleural effusion by pleural invasion. They may show associated distant or general pathology, such as enlarged superficial lymph nodes, typical blood picture, positive marrow biopsy, or splenic enlargement as the case may be. These tumors are exquisitely radiosensitive and rapidly melt away with treatment. The clinical history, x-ray appearance, response to x-ray therapy, and associated specific findings usually enable an accurate diagnosis to be made. *X-ray therapy* is a valuable palliative.

Thymic tumors are found in the superior and the anterior mediastinum, immediately under the manubrium sterni. Benign thymic hyperplasia is not rare in children. It responds rapidly and permanently to x-ray irradiation. The malignant thymoma is a very malignant tumor resembling lymphosarcoma, usually appearing in young adult life. It is also very radiosensitive but recurs and causes death. It, too, may involve the pleura and cause bloody effusion. There are other thymic tumors, apparently benign, occurring in adult life. A certain number of them have been found to be associated with myasthenia gravis. Clagett<sup>99</sup> has stressed the frequency of abnormalities of the thymus in this disease even when an actual tumor is not present. He reports on 20 cases of *thymec-*

**tomy** for myasthenia gravis, found in the literature, with 4 deaths. About one-half of the cases were appreciably improved. He is willing to recommend thyrmectomy in these cases when an actual tumor is present. In other cases, **irradiation** of the gland might be worth while.

Thyroid tumors may be present in the mediastinum. Usually they are substernal and located in the upper anterior mediastinum. They are usually adenomatous and often contain cystic areas. While aberrant thyroid tissue may be found in this area, most cases are descended from the cervical region and carry their vascular pedicle down with them. In one of the author's personal unreported cases a large posterior mass located behind the aortic arch turned out to be an intrathoracic adenomatous thyroid which had descended from the cervical region carrying its blood supply with it.

Tuberculoma of the mediastinum, such as reported by Grace,<sup>100</sup> and large caseous mediastinal lymph nodes occasionally give a picture similar to Hodgkin's disease or lymphosarcoma. However, they are not rapid growing and are resistant to irradiation. There may be associated tuberculosis in the lungs or elsewhere. Probably these masses should be removed surgically.

Aneurysms make up an appreciable number of the roentgenographic mediastinal tumors. They usually arise from the ascending aortic arch but may arise from carotid, innominate artery, subclavian, any part of the aorta, from the pulmonary artery or ductus arteriosus when present. Diagnosis may be made by fluoroscopic study, by opacification of the vascular tree with diodrast or similar material, and by ordinary clinical findings: Tracheal tug, different arterial pressures in each arm, luetic lesions, etc.

Treatment for aneurysms varies with the location and type of dilatation. The innominate, subclavian, and left common carotid have been treated by **proximal and distal ligation**. Serious complications often attend such operations (softening of the brain, atrophy or gangrene of the arm, etc.). Harrison and Chand<sup>101</sup> report a case of aneurysm of the left subclavian artery cured after a lapse of 19 months' time by application of cellophane about the artery proximal and distal to the aneurysm.

For saccular aneurysms approaching the chest wall, **wiring** is fairly satisfactory. An insulated needle is inserted through the chest wall into the aneurysmal sac. Special gold-copper alloy wire is inserted through the needle into the aneurysm. It kinks and curls up in the sac. After 10 to 12 feet of wire have been inserted, an electric (galvanic) current is passed through the wire until coagulation has occurred about the wire. This acts as a scaffolding for further clotting and perhaps obliteration of the sac. Pain is usually promptly and permanently relieved by this wiring.

**Carotid-jugular anastomosis** as proposed by Babcock produces a large arteriovenous shunt. It drops the arterial blood pressure and increases the speed of circulation so that the hydrodynamics of the circulation are changed to lessen the distending effect of the blood on the dilated aneurysmal region. The large arteriovenous shunt causes a great increase in cardiac work leading to hypertrophy and dilatation. There may be interference with the cerebral circulation.

### Mediastinal Tumors of Neurogenic Origin

Lee and Ritter<sup>102</sup> have classified them as follows: (a) Malignant sympathangiomias; (b) benign ganglioneuromias;

(c) chromaffinomas; (d) malignant neuroblastomas.

Tumors of the last group occur in infancy and childhood. The symptoms are negligible until they produce pressure on the surrounding structures.

Schaffner, Smith, and Taylor<sup>108</sup> report three cases of neurogenic tumor in the posterior mediastinum, successfully removed. One of these appeared in the superior mediastinum and produced Horner's syndrome, thus simulating the so-called superior pulmonary sulcus syndrome of Pancoast.

These tumors arise posteriorly in the mediastinum either from the sympathetic ganglionated trunk or from the spinal nerves. In some cases these latter may be "hour-glass" or "collar-button" in shape, with part of the tumor situated within the spinal canal, and connected to the outside tumor by a small "waist" lying in the intervertebral foramen.

These tumors are usually well encapsulated, oval or rounded in shape, lie in the posterior mediastinum in close relationship to the heads of the ribs and the bodies of the vertebrae. They are usually slow growing, particularly the benign ones. Symptoms are often absent, the diagnosis being made because a chest x-ray was taken for some other reason. They are not usually adherent to the lung, and a diagnostic pneumothorax will reveal the extrapulmonary location. They are easily removed surgically by *enucleation* in most cases. Occasionally rib destruction occurs and this requires block resection of the involved portion of chest wall.

Blake and Bradford<sup>105</sup> discuss fibrosarcoma of the chest wall and describe a case in a 20-year-old white male following trauma of the chest wall. These are slow-growing tumors which are operable for a long period of time.

Pneumothorax will usually show the extrapulmonary location. These authors feel that this case illustrates the need for careful follow-up of cases of trauma, especially where fractures exist. Persistence of pain beyond the expected period of healing, or the appearance of a lump over a fracture site should suggest the possible development of a tumor due to trauma.

### Congenital Cysts of the Mediastinum

Carlson<sup>106</sup> has presented an excellent classification of congenital cysts of the mediastinum with a description of their respective usual courses and possible etiology. He divides these cysts into eight groups: (1) Epidermoid cysts—derived from ectoderm; (2) dermoid cysts—derived from ectoderm and mesoderm; (3) teratomas—derived from all three primitive germinal layers; (4) cystic lymphangiomas—derived from mesoderm; (5) pericardial coelomic cysts—derived from mesoderm; (6) bronchial (bronchiogenic) cysts—derived from entoderm and mesoderm; (7) gastric (gastrogenic) cysts—derived from entoderm and mesoderm; (8) enteric cysts (enterocystom)—derived from entoderm and mesoderm.

The first three groups have usually been lumped together in clinical descriptions as dermoids or teratomas. They have been explained in two ways—one that a secondary anlage develops in the body either through the fertilization of a polar body or the independent development of a blastomere. The other assumes that there is an abnormal segmentation of cells at some stage of embryologic development. The origin of mediastinal teratomas is the region of the bronchial clefts, the abnormal cellular inclusions being carried into the anterior mediastinum with the descent of the heart.

These cysts usually occur in the anterior mediastinum and may protrude laterally. They may extend from the superior mediastinum into the base of the neck. They are usually lined by stratified squamous epithelium and contain hair and sebaceous material. They may contain teeth, bone, cartilage, glands, etc.

They grow slowly over a period of many years before giving symptoms. Dyspnea, cough, and pain are common early symptoms. If a communication develops into a bronchus, infection of the cyst may occur, and hair and sebaceous material may be expectorated. Some of these tumors become malignant. In view of the good general condition which is usually present when this condition is first diagnosed, a *one-stage complete removal* is recommended. Heuer and Andrus have shown that this method gives an excellent chance for complete cure. In cases where the patient is in poor condition or the cyst is infected, drainage of the cyst by marsupializing it to the skin will relieve the symptoms. For complete cure, later removal of the cyst wall is necessary.

*Cystic lymphangiomas* are rare. Multiple cysts are formed, containing clear, brownish, or gelatinous material, and lined by a single layer of endothelium. Skinner and Hobbs suggest that they may be formed from a portion of the anlage for vessel formation drawn down from the region of the gill clefts by the pericardium in its descent. Some think they derive from the thymus. The tumor of the posterior mediastinum reported by Aguilar and Tueirel<sup>107</sup> which they called a cystic fibromyxolipo-lymphangioma probably belongs in this group.

*Pericardial coelomic cysts* are simple thin-walled cysts containing clear, thin fluid, lined by endothelium or mesothelium, and in close association with the pericardium. Lambert has reported two

such cases and believes that they develop from one of the several primitive pericardial lacunae which fails to merge with the others.

The "spring water cyst," such as described by Greenfield, Steinberg, and Touroff<sup>108</sup> probably fits this classification.

*Bronchial cysts* usually contain the cellular elements normally found in the bronchial or tracheal wall. The origin of these tumors is subject to dispute. They may be due to a pinching off of a diverticulum from the foregut in the region of the tracheal bud. Or there may be a secondary budding of the tracheal bud. Or there may be imperfect closure of the communication between the trachea and esophagus.

They usually appear in the posterior mediastinum, usually in the region of the tracheal bifurcation. There is seldom communication of the lumen with the tracheobronchial tree.

Ordinarily symptoms are produced early in life, perhaps in the newborn. They may compress trachea or bronchi or esophagus, and cause atelectasis, dyspnea, dysphagia, perhaps sudden death (even stillbirth). Coughing may be persistent or spasmodic. The case described by Marshall and Cookson<sup>22</sup> from autopsy in an infant is typical.

The small size of the cyst and its location makes x-ray diagnosis difficult. Bronchoscopy and bronchography should be employed.

*Gastric cysts* are rare. They contain viscid fluid which may contain hydrochloric acid, and are lined by mucosa similar to that of the stomach. They frequently are large in size and are located in the posterior mediastinum, usually deviating to one side. Peptic ulceration and even perforation may occur.

The origin may be ascribed to a pinched-off diverticulum of the foregut,

to germ cells of the esophagus capable of producing gastric mucosa, or to a vestige of the omphalomesenteric duct.

Because of their large size, these tumors may be detected by physical examination. X-ray will usually reveal a rounded posterior mediastinal mass unless atelectasis or pleural fluid obscures the view. Aspiration of the cyst contents may permit finding of hydrochloric acid, which is pathognomonic.

Schwarz and Williams<sup>109</sup> report two cases, one of which contained hydrochloric acid. The other did not. Symptoms usually occur in the first few weeks or months of life, and are either due to pressure (dyspnea, cough, cyanosis, dysphagia) or respiratory infections (perhaps from atelectasis), or both.

*Enteric cysts* are similar to gastric cysts, but are lined by intestinal mucosa. They are very rare. To date the four or five found have appeared in infants at autopsy.

Carlson<sup>106</sup> reports a case of teratoma and a gastric cyst cured by operation. The latter was done in two stages, the first stage being a drainage operation to relieve pressure symptoms. The drainage tract became digested and eroded much like a gastrostomy opening between stages.

He also reports a bronchiogenic cyst diagnosed at autopsy.

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## CARDIOVASCULAR SYSTEM

### Patent Ductus Arteriosus

This condition, which is physiological at birth, in some cases persists throughout life. In many instances the communication is very small and may be found at postmortem without ever having given symptoms or having been suspected during life. In these cases it is probable that there has never been any appreciable shunt of blood from the aorta

to the pulmonary artery. In other cases the ductus remains widely patent throughout life. The greater arterial pressure in the aorta then forces blood across the ductus in a direction the reverse of the flow during fetal life. This amounts to a large arteriovenous communication. The cardiac work is greatly increased, often several hundred per cent. Cardiac hypertrophy and dilatation ensue and congestive failure can appear without other organic cause. Patent ductus arteriosus may be associated with other cardiac abnormalities and anomalies, and sometimes has a compensatory rôle.

The second great danger in cases of patent ductus arteriosus is the possible development of subacute bacterial endarteritis of the ductus. Estimates of its frequency are undependable, but there is no doubt that it does occur. The *Streptococcus viridans* is the usual bacterial agent concerned.

**Symptoms**—Generalized physical underdevelopment, and a tendency to dyspnea have been described. Cyanosis is rarely present.

**Signs**—The finding of a large heart and a loud systolic murmur at its base are fairly constant. Often the murmur may extend throughout the entire cardiac cycle, with perhaps a humming or machinerylike quality, with systolic accentuation. A low diastolic pressure and a Corrigan pulse are frequently found.

**Diagnosis**—This is made by the clinical history and findings, plus the x-ray. The six-foot x-ray chest plate shows pulmonary congestion. Cardiovascular opacification with diodrast reveals an outward bulging or tenting of an area on the lesser curvature of the aorta. This tenting is not often at the point of attachment of the ductus to the aorta, and its causation is not well understood.



**Prognosis**—The danger of cardiac dilatation and failure is proportionate to the size of the shunt, and may be estimated reasonably accurately. The danger of subacute bacterial infection cannot be accurately estimated at present. Extremely few cases of patent ductus arteriosus reach advanced age if they are sufficiently severe to be diagnosed.

**Treatment**—The logical treatment is *ligation of the ductus*, preferably division between ligatures. The operation is done through an anterior incision in the second left interspace. The technic is simple unless the ductus is very short and broad. The mortality is not well determined because too few cases have been operated upon for accurate statistics, but should be very low. If the ductus cannot be safely ligated, it may be *wrapped with cellophane*. The resulting fibrosis and stenosis will gradually produce complete occlusion. At least one case has been successfully so treated by Meade and Harper.<sup>90</sup>

Touroff<sup>91</sup> has now reported eight cases of patent ductus arteriosus with superimposed subacute *Streptococcus viridans* endarteritis, treated by ligation or ligation and division of the ductus. In all 8 cases the organism was consistently obtained from the preoperative blood cultures. In the first four cases one was completely successful, two died on the operating table because of operative rupture of the diseased ductus, and one survived but continued to have positive blood cultures. In the second series of four early cases, *chemotherapy* failed in all cases. Ligation in three, and ligation and division of the ductus in the other, produced four clinical cures. It is interesting that blood cultures become negative immediately after ligation of the ductus, often in 15 minutes. Touroff suggests that this may be due to the

diversion of the systemic arterial pressure which had been forcing eddies of blood through the ductus. These swept off bacteria and carried them through the dilated pulmonary vascular system at high speed and pressure. The normal pulmonary filter which is highly efficient in removing bacteria from the circulating blood is dilated in patent ductus arteriosus and permits the organisms to pass through into the systemic circulation. Ligation of the ductus prevents the aortic blood from swirling against the vegetations and so very few bacteria are swept away into the pulmonary arteries. Those which do enter the pulmonary vascular system are picked up by the pulmonary capillary filter which is no longer distended by the abnormally high arterial pressure. They are then phagocytosized. These organisms are of low virulence and are soon destroyed, even in the vegetations of the ligated ductus. It is important that these cases be subjected to ductal ligation early before the infection has caused extreme thinness and friability of the ductus wall. In view of the extreme hopelessness of these cases, ductal ligation certainly seems worth while for subacute bacterial endarteritis.

### Coronary Arteriosclerotic Disease

This is a common affliction, particularly of men past middle life. The cause is not known, but the disease is believed to be much more common in executives and those subjected to mental and emotional strain than in persons who do manual work. It is often associated with hypertension.

The coronary arteries become the site of atheromatous plaques and generalized thickening of the subintimal tissues. Thrombosis is common. If thrombosis occurs in a large coronary branch sudden death is usual, since there is relatively little anastomosis between the various

coronary branches. Thrombosis in a smaller branch causes an area of infarction in the myocardium, often extending either to the epicardium or to the endocardium. If the coronary occlusion takes place gradually, adequate collateral circulation can develop, both from the other coronary vessels, and also from the septal blood supply. The septal and sinusoidal system of vascular channels and spaces is much more important in lower animals than in man, but even in man can be developed gradually to the point of replacing the entire coronary system, as shown by occasional autopsy findings of cases with both coronary arteries completely obliterated.

Angina pectoris is a sudden, sharp, severe sensation of pain or pressure in the substernal region, characteristically radiating to the back and down the left or both arms, which appears in many of these cases of coronary arteriosclerotic disease. It has been likened to the pain of intermittent claudication in arteriosclerosis of the tibial vessels, and it usually is initiated by effort. Sometimes it appears at rest or even in sleep (angina decubitus) and is then of much more serious import. Some men believe that every attack of angina pectoris is a slight attack of coronary thrombosis. This seems to be an extreme view. Others feel these attacks are due to a spasm of the constrictors of the coronaries, perhaps due to sympathetic imbalance or storm. Others consider the anginal syndrome to be merely a painful response to myocardial anoxemia.

**Treatment**—In any case, there is considerable evidence that during an anginal attack ventricular fibrillation is apt to appear and is usually promptly fatal. Therefore, any dependable method of preventing or avoiding these attacks is desirable. In addition, angina pectoris is

a painful and distressing symptom. If only for this reason, we would like to have a method of symptomatic prevention. The *nitrites* give prompt relief of the attacks after they have occurred, but do not prevent them.

Block of the upper four dorsal and perhaps the inferior cervical sympathetic ganglia by *alcohol injection* is very effective in preventing the anginal pain. Whether it truly prevents the attacks or just makes them painless is a disputable point. Unfortunately, a fairly large percentage of these persons develop a severe alcoholic intercostal neuritis from the injection, which may be more troublesome than the angina. *Resection* of these ganglia is a more dependable procedure and is not accompanied by neuritis.

*Total thyroidectomy* for angina pectoris is very effective in relieving the painful attacks. But the myxedema which may result is a serious disease, hardly preferable to angina pectoris. These patients would have to remain constantly under strict medical control, indefinitely, so that thyroid therapy could be regulated to keep their metabolisms above the myxedema level and below the angina level. Strict coöperation of any patient for a prolonged period cannot be depended upon, especially in these days of frequent changes of residence and occupation.

Since coronary sclerosis causes myocardial ischemia and since the anginal pain is probably related to a more severe ischemia, it would seem logical that any method which would increase the myocardial circulation would relieve the condition. This has long been attempted medically by the vasodilator and sedative drugs (*nitrites, aminophyllin, papaverine, atropine, theobromine, alcohol, the barbiturate sedatives*). Results

are thus obtainable, particularly in mild cases.

Surgically, there have from time to time been various operations proposed to bring a new blood supply to the myocardium, especially by *grafting a vascular tissue to the epicardium*. Beck applied a pedicled flap of pectoral muscle to the heart after removing the epicardium with a burr. O'Shaughnessy brought the omentum up through a diaphragmatic incision, and sutured it to the epicardium. The lung has been employed as a vascular graft to the surface of the heart. Mobilized intercostal bundles have been proposed.

It has been thought that the circulation of the pericardium might be increased under certain conditions, and be available to nourish the myocardium if *vascular pericardial adhesions* could be produced. Various substances, such as *bone meal*, *aleurnot*, and *talc*, have been used to produce adhesions. Unfortunately, these adhesions are not always very extensive and vascular anastomoses between the graft and the myocardium are not always demonstrable. Anyway, how can one tell which way the blood travels in these vascular anastomoses? It seems probable that, in at least some phases of cardiac contraction, the direction of blood flow would be away from the heart and toward the graft. Another pertinent question is how large an increase in myocardial vascularity can we hope to add by means of a graft? Granted that these persons are not to be allowed any strenuous physical activity, still the myocardial circulation in healthy persons at full strenuous activity may take something like 10 per cent of the entire cardiac output. It would be reasonable to consider that any important additional vascularization should be of somewhat the same order. Since none of these proposed grafts have in themselves anything

like this circulation and since only a fraction of it can possibly be added to the myocardial blood supply, it would seem that there is grave question of the effectiveness of any grafting procedure. Another disturbing thought is the anatomical arrangement of the layers of the myocardium, each with its own layer of coronary branches. How much increase can be expected in the coronary circulation of the deeper myocardial layers even if a considerable increase is produced to the superficial layers by means of a graft? We know that death can take place from an infarct of the deeper myocardial layers even though the superficial layers are intact.

Louis Gross proposed ligation of the coronary vein to develop the septal and sinusoidal vascularization of the deeper myocardial layers. However, animal experimentation has not seemed to bear out his original idea that this procedure would protect against death from a subsequent ligation of a major coronary artery. This work was done in animals where the septal and sinusoidal circulation normally play a somewhat more important rôle in myocardial nutrition than is the case in humans.

However, in spite of all these objections there has been one constant clinical observation—after almost any of these operations there is marked and prolonged relief from anginal pain. Whatever the explanation, with even the simplest proposed operation—Samuel Thompson's *pericardial poudrage with talc*—the work tolerance of the patient was always greatly increased before pain would appear. This not only made life more tolerable, but it often made possible a return to productive occupation.

This clinical observation has led to the thought that perhaps the irritation of the procedure or the chemical agent employed might cause development of inter-

coronary communications, since it seemed that the benefit from the very minor (poudrage) procedure was clinically as great as that from the very major operations (which carry an appreciable mortality). Schildt, Stanton, and Beck<sup>111</sup> investigated the effects of different substances applied in the pericardial cavity of dogs in developing demonstrable intercoronary circulation in dogs. The method of demonstrating these communications was as follows: The anterior descending branch of the coronary artery was ligated at its origin. A mixture of barium in gelatine was now introduced at a temperature of 45° C. and 200 mm. mercury pressure through cannulae into the right coronary artery and the circumflex branch of the left coronary. The appearance of barium in the anterior descending branch (demonstrable by x-ray) was considered evidence of increased intercoronary circulation.

Many of the substances used in the study (croton oil, formalin, iodine) were too irritating and caused death of the animals. Others produced much pericardial effusion and sometimes pericardial tamponade. Others caused development of chronic constrictive pericarditis. Finally, of those which avoided the above disadvantages, only a few caused development of demonstrable intercoronary communication and usually this was inconstant. Talc was not dependable in producing these communications. Of all the substances employed, **powdered asbestos** was most satisfactory. One-tenth to 0.2 Gm. spread evenly throughout the pericardium always led to the development of pericardial adhesions and good intercoronary communications. In some cases the animals were subjected to ligation of the anterior descending branch of the left coronary artery some time after the asbestos application. Mortality of this procedure in these animals was

33 per cent; that of normal controls was 70 per cent. It would seem that the introduction of powdered asbestos into the pericardial sac dependably increases intercoronary communications and protects to a considerable extent against future attacks of myocardial infarction.

### **Intrapericardial Teratomas**

These are rare tumors. They may become very large and cause cardiac embarrassment by pressure, or respiratory embarrassment by taking up a great deal of room in the thorax. They are usually attached by a vascular pedicle in the region of the great vessels at the base of the heart. Gebauer<sup>112</sup> has reported one in which staphylococcic infection had occurred, which was drained and later resected in stages. Unfortunately, injury of the aortic wall by a toothed clamp on the vascular pedicle led to death from hemorrhage. Beck<sup>113</sup> has reported a case successfully operated.

### **Chronic Constrictive Pericarditis**

This is a condition in which, due to fibrous thickening or calcification of the pericardium, there is great interference with diastole. Therefore, filling of the chambers is greatly impaired, and the cardiac output is markedly reduced.

**Etiology**—This is frequently doubtful, but may be tuberculous pericarditis, rheumatic pericarditis, polyserositis, or pneumococcic pericarditis. Jager and Ransmeier<sup>114</sup> have recently reported a case caused by the *Bacterium tularensense*. Pericardial effusion in cases of tularemia is uncommon.

**Symptomatology**—Enlargement of the liver and ascites are usually the most prominent symptoms. Edema of the feet and ankles is often present. Dyspnea is less marked than one would expect in the presence of these other signs of congestive failure. The veins of face and neck are engorged.

The physical examination reveals a relatively low systolic blood pressure in most cases, with a high diastolic pressure (low pulse pressure), a quiet heart, often small. Auricular fibrillation is fairly common. The paradoxical pulse (weakening or absence of pulse on deep inspiration) is nearly pathognomonic and usually present. The descent of the diaphragm elongates the oval pericardium and, since it is inelastic, its volume becomes smaller and this can only occur by squeezing or wringing out the heart, thereby reducing its output.

Venous pressure is markedly elevated, often to 30 cm. water.

Fluoroscopy reveals limited or absent movements of the heart, and usually a small heart. X-rays will reveal calcification of the pericardium in 14 per cent of cases. This is particularly well visualized in the lateral x-ray film.

**Treatment**—Therapy is *pericardiectomy*. This is undertaken through an incision in the left thorax, usually after removing portions of the fourth and fifth and possibly sixth ribs and their cartilages. The pericardium should be removed first over the left ventricle, then over the right. It is questionable whether it should be removed over the auricles. Rarely, the vena cavae may be seriously involved in the process and it may be necessary to remove the adventitia—a very dangerous procedure. An especial effort should be made to avoid injuring the phrenic nerve. It is important to avoid removing too much pericardium at one operation. These operations may always be repeated if insufficient removal is accomplished the first time. The power of the heart to hypertrophy eccentrically is greater than ordinarily realized.

Harrison and White<sup>115</sup> have reported a follow-up study of 37 cases of constrictive pericarditis; five were caused by tuberculous pericarditis; two followed

pneumonia and polyserositis; cause was unknown in 29. Twenty-two presented a normal rhythm; 14 had auricular fibrillation, and one auricular flutter. Twenty-eight cases were subjected to pericardiectomy; 14 of these became clinically cured, and five died as a result of operation; three operative cases were markedly improved; two died at a later date from the primary disease (tuberculosis, rheumatic heart disease); four died at some time after operation of causes not related to the cardiac condition; nine cases were not operated, mainly because the patient or his family would not consent.

### Adhesive Pericarditis

Intrapericardial adhesions which bind the epicardium to the pericardium are common. Often they are mere tenuous bands or strings. Sometimes they are local areas of direct symphysis of pericardium and epicardium. Occasionally, there is a complete obliteration of the pericardial space by fibrous union of the layers. In the absence of any tendency to constrictive pericarditis there is relatively little interference with cardiac function.

Extrapericardial adhesions also are by themselves of little importance. They are always present to a considerable degree in every case which has recovered from an empyema or mediastinitis. They hamper cardiac action only slightly.

But the combination of extensive intrapericardial and extrapericardial adhesions puts a very serious load of extra work upon the myocardium. The precordial region and the diaphragm are forcibly pulled upon with every cardiac cycle. Hypertrophy and dilatation always follow this combination of pathologies if it is at all severe. By removing the ribs, periosteum, the overlying costal cartilages, and perhaps a portion of the width of the sternum (on the left side)

these cases may be much helped (*Brauer operation of cardiolysis*). Phrenic paralysis on that side further improves heart function.

### Extreme Cardiac Enlargement

The same operation is sometimes performed for a different cause. Great enlargement of the heart is not uncommon in valvular and other cardiac disease, both due to hypertrophy and dilatation. The distance between the sternum and the anterior surface of the bodies of the vertebrae is limited. When cardiac enlargement reaches the limits of this distance there is serious interference with its function, and this further aggravates the symptoms. By removing the bony and cartilaginous support of the precordium, the heart may bulge forward and its function improve. Often congestive failure will dramatically disappear after such a procedure. But the underlying organic heart disease associated with so much enlargement still remains and so not too much recovery should be expected. Newton and Levine<sup>116</sup> report such a case in which dysphagia and congestive failure were much diminished by resection of the bones of the precordium.

### Nonpurulent and Purulent Pericardial Effusions

Nonpurulent effusions are probably fairly common but most of them are of small size and are resorbed without the diagnosis ever being made. Probably every case of coronary thrombosis and every case of rheumatic fever is associated with some pericardial effusion. However, there are cases with large effusions, some of which may cause symptoms of pericardial tamponade. There are also cases of very persistent serous effusion.

Most of these cases are today treated by *pericardicentesis* through an aspi-

rating needle. This may be introduced through the so-called "free" or extrapleural space to the left of the sternum, usually the fourth or fifth interspace close to the sternal margin. A better place for aspiration is at the junction of the xiphoid and seventh costal cartilage on the left. The needle is directed upward at a 45 degree angle and enters the pericardial space in the diaphragmatic region. This approach is surely extrapleural, should be extraperitoneal, and, if the heart is accidentally punctured, the danger of coronary vessel injury is slight. However, these dangers are not entirely eliminated, and it is impossible to empty completely the pericardium by a needle.

Donaldson<sup>117</sup> recommends a *valvular type of drainage* in nonpurulent pericardial effusion. By this means complete evacuation of the pericardial cavity is produced and it persists long enough to permit healing to take place, usually by obliteration of the space. He makes a small transverse incision over the left rectus muscle, about 1½ inches below the xiphoid—sternal junction. This includes the anterior sheathe of the rectus muscle. The muscle is dissected from its sheathe and retracted laterally. The dissection is continued anterior to the transversalis fascia and upward until the pericardium is reached. It is opened and the pericardial fluid escapes. A small, flat, soft rubber drain may be left from pericardium to skin. The rectus muscle is allowed to slip back into its normal position, thereby producing a valvular drainage which prevents secondary infection of the pericardium. By keeping the patient on his abdomen, complete drainage of the effusion may be obtained. The rubber drain should be removed within three to four days.

In suppurative pericarditis, Donaldson does not recommend this technic, but

suggests an *anterior drainage* after removing the fifth, sixth, or seventh rib cartilage. He advises *irrigation* in these purulent cases.

### Valvular Heart Disease and Congenital Defects

With the exception of obliteration of the patent ductus arteriosus, little clinical success has attended surgical attempts to correct acquired or congenital valvular defects or septal defects. Many cases have died on the operating table; very few have been improved. It would seem that considerably more experimental work must be done on animals, both in the production of these lesions and in their treatment after full development.

Adams, Rasmussen, Hrdina, Shaw, and Aronson<sup>118</sup> have recently described a series of experiments upon dogs in which they have produced both stenosis and regurgitation of all four cardiac valves. They were able to visualize each of these valves by controlling the entrance of blood to the heart by sutures passed as slings about the superior and inferior vena cavae. The stenoses were produced by suturing the valve leaflets together or by circular ligatures about the chordae tendinae. Operations on the right heart were tolerated much better than those on the left. Blood loss in left-sided operations was considerable, since it was necessary to permit a considerable flow of blood through the chambers when operating on this side. Otherwise, air embolism was common and usually fatal.

Harken<sup>119</sup> has also reported a series of animal experiments in which he was able to produce typical subacute bacterial endocarditis. By surgical operation 16 animals were subjected to injury of the valve leaflets; four died from operation. The other animals then spontaneously developed subacute bacterial endocarditis with positive blood cultures, irregular fe-

ver, and embolic phenomena. Apparently the infecting streptococci were autogenous in the blood. In eight control cases the development of subacute bacterial endocarditis was prevented by preoperative and postoperative administration of *sulfonamides*.

### Chronic Fibrous Mediastinitis

Chronic fibrous mediastinitis with obstruction of the superior vena cava has been described by Erganian and Wade.<sup>138</sup> In these cases a nonspecific fibrous thickening occurred in the mediastinum with gradual obliteration of the superior vena cava which eventually became an obliterated fibrous cord. The cases presented the typical symptoms of superior vena caval obstruction with engorgement and high venous pressure in the veins of the head and upper extremities, the development of dilated superficial collateral venous channels, edema of face and arms, dizziness, easy dyspnea, and facial and upper extremity cyanosis. There is no satisfactory therapy but it is important to differentiate the lesion from vena caval obstruction by neoplasms.

### Pulmonary Embolism

This is a frequent and serious postoperative complication in certain types of surgical cases. Gastrectomies, colectomies, septic pelvic operations are particularly likely to be complicated by thrombosis, septic or otherwise, of the veins draining into the inferior vena cava. By the time the patient is able to be out of bed, these thrombi are well formed, and are often loose in the lumen. If small pieces of thrombus break off, they travel to the right auricle and ventricle, and are then pumped into the pulmonary arterial system, where they block the smallest arterial branch which will still accommodate them. A simple or septic pulmonary infarct is then produced (de-



pending on whether the embolus was sterile or septic).

If the embolus is a large one, it may block an entire main branch of the pulmonary artery. It then often causes sudden death. Occasionally the embolus lies as a "rider" across the pulmonary arterial bifurcation. These latter also commonly cause death.

Now it is necessary in performing total pneumonectomy to ligate one of the two main divisions of the pulmonary artery and this never causes sudden death. It would seem that there must, therefore, be some other factor which causes death in cases of obstructive embolism of just one main pulmonary arterial branch. Jesser and DeTakats<sup>139</sup> believe that the lodging of an embolus in a large pulmonary artery sets up reflexes which produce extreme spasm of the bronchi and bronchioles. They believe that this is the mechanism causing death. They recommend giving *atropine*, 0.001 Gm. ( $\frac{1}{60}$  grain), or *papaverine*, 0.03 Gm. ( $\frac{1}{2}$  grain), in clinical human cases, to treat pulmonary embolism. In view of the high mortality and the relative unavailability of prompt pulmonary embolectomy in these cases, it would seem well worth while to make further clinical investigation of this method of treatment.

## ESOPHAGUS

### Congenital Atresia of the Esophagus

This is a failure of proper development of the foregut and often of the lung buds. The possible varieties of defect are: (a) The esophagus may be relatively normal in size and position but have an anomalous communication with the trachea or one of the major bronchi; (b) or the upper end of the esophagus may empty into the trachea, and the lower end be missing or a blind pouch

from the stomach up into the thorax; (c) or both portions of the esophagus may be separate but communicate through the tracheobronchial tree to which they both communicate; (d) or both ends of the esophagus may end as blind pouches; (e) commonly, the upper end of the esophagus is a blind pouch and the lower end communicates to the trachea or a main bronchus either directly or through a long narrow tube (SEE: Fig. 5).

All of these defects seriously interfere with feeding, and all of them tend to produce aspiration pneumonia because mouth and/or gastric contents are constantly being aspirated into the tracheobronchial tree. Whatever is done for these infants must be done quickly (within a very few days) if any chance for life is to be given.

**Diagnosis**—Regurgitation of feedings and the onset of cyanosis, dyspnea, and coughing with each attempt of feeding should make one suspicious of the possibility of an abnormality of the esophagus. Immediately, visualization of the esophagus by administering lipiodol (not barium, which will cause aspiration pneumonia) under the fluoroscope should be undertaken. At least the upper portion of the esophagus will be observed and the presence or absence of a tracheobronchial communication observed. The lower segment of the esophagus may also be visualized in some types. The presence of communication of the lower segment to the air passages is proven if there is gas in the stomach or intestine on flat x-ray of the abdomen. If no gas is present, such a communication still may be present. Chont and Starry<sup>120</sup> report this to be present in at least 90 per cent of cases.

**Treatment**—Some men have merely employed a *gastrostomy* for feeding and to improve the infants' general condition.

While this may take care of the feeding problem, the eventual onset of fatal aspiration pneumonia is inevitable, since even in the absence of any tracheal communication, there must be constant overflow of mouth secretions into the larynx. As a preliminary procedure before more

into the trachea and bronchi. This stage may be done by either an abdominal or a thoracic approach; (b) the upper esophageal segment is exteriorized to permit drainage of pharyngeal secretions on to the skin of the neck or anterior chest; (c) later plastic operations to reestablish

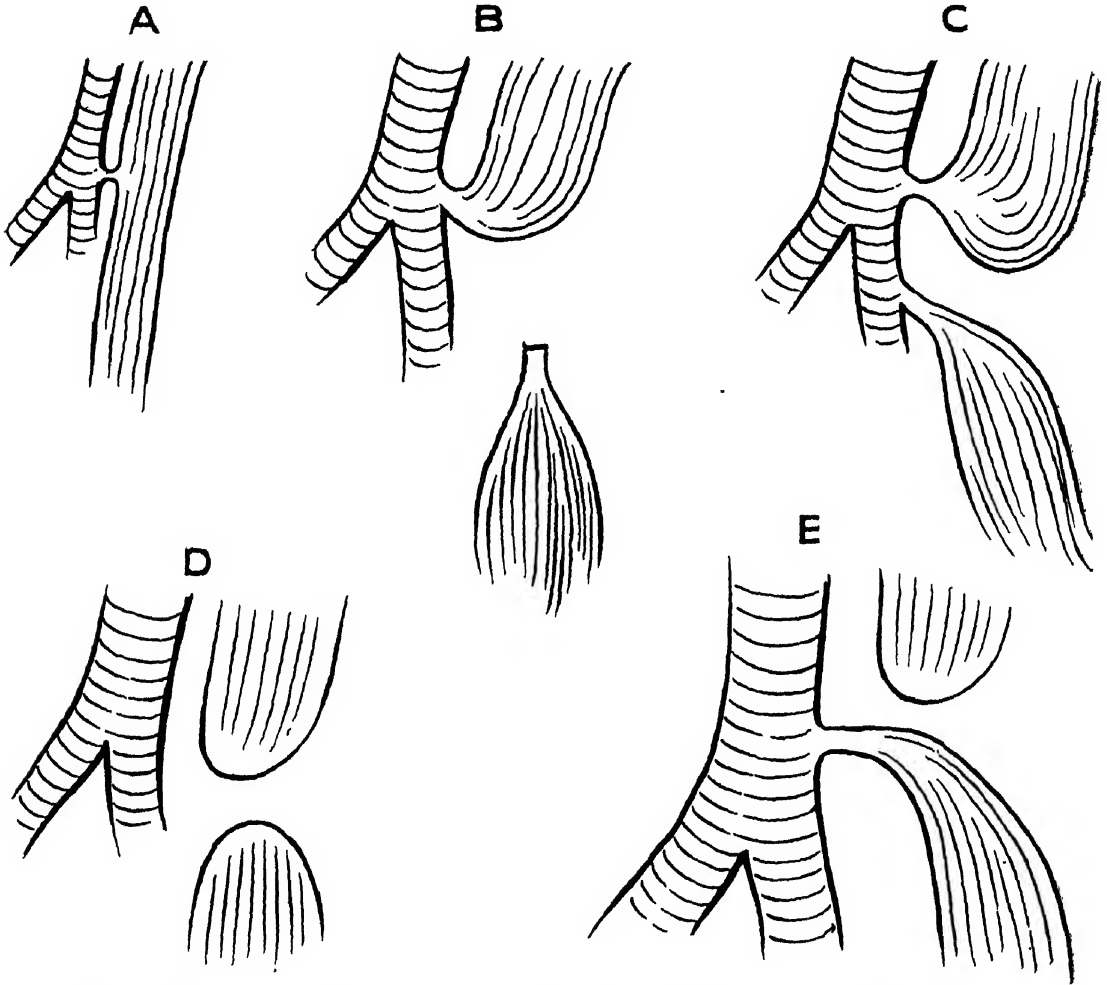


FIG. 5.—The five possible anatomical arrangements in congenital atresia of the esophagus.

major intervention, it may be considered part of a planned, staged operation.

Haight and Towsley<sup>121</sup> have considered this problem in great detail. They describe the two general methods of surgical attack. In the first or indirect method the procedure is staged somewhat as follows: (a) A gastrostomy is done along with ligation or exteriorization of the distal esophageal segment to prevent regurgitation of gastric contents

gastrointestinal continuity by forming a skin lined tube or a cutaneojejunal tube.

The method they prefer is a direct attack in which an attempt is made to anastomose the upper and lower ends of the esophagus after closing the fistulous communications (if any) to the air passages. This may be done either transpleurally or extrapleurally. These authors prefer the latter to avoid the risk of empyema, should the suture line leak.

These anastomoses are usually technically possible but are liable to leak or separate because of the probability of tension on the suture line during crying and straining, and also because of the lack of a serous coat on the esophagus. The low vital capacity in very young infants impairs their ability to tolerate an empyema.

They report 15 cases of congenital atresia of the esophagus admitted to the hospital during the past seven years. All had a blind upper esophageal pouch, and at least 14 had a fistulous communication of the lower segment of the esophagus to the air passages.

Of the 15, 7 were operated upon and a *direct anastomosis* was accomplished in five of them through the extrapleural approach. In one case simple extrapleural ligation of the fistula and gastrostomy were performed. In another, due to lack of air in the stomach, it was believed that no lower fistulous tract existed. Simple gastrostomy was done. Later, vomiting caused fatal aspiration pneumonia, proving that a fistula did exist into the trachea or bronchus.

There was one successful case following direct anastomosis. The child was in good health, with a slight esophageal stricture at the site of anastomosis, two years after operation. There had been some temporary leakage at the anastomotic site in this case, too.

### Pedunculated Tumors of the Esophagus

Samson and Zebman<sup>122</sup> have reviewed the literature and found only 25 cases reported. The common histological make-up is that of a leiomyoma. Several of these have undergone malignant degeneration or there has been malignancy in the overlying mucosa. Leiomyomas may be found largely extending outward from the wall of the esophagus, or may be

intramural, or more commonly extend into the lumen as pedunculated masses. They are usually covered by mucous membrane which may show ulceration in places. The esophageal lumen gradually enlarges as the tumor grows, and there is practically never any esophageal obstruction.

In most cases it would be feasible to resect the tumor locally by longitudinal elliptical incisions in the esophageal wall. The enlarged lumen and excessive mucous membrane would permit primary closure of the defect without any tendency to stricture. Because of the lack of a serosal coat to the esophagus and the possibility of leakage, an *extrapleural operation with drainage* would seem preferable to a transpleural one. In cases where local resection by esophagotomy is not feasible by reason of size or location of the growth, or because of malignant change the case should be treated by the methods employed for esophageal carcinoma.

Brock<sup>123</sup> reports a case of myoma of the lower esophagus extending into the stomach. He treated it successfully by a one-stage partial *cardioesophageal resection with primary esophagogastric anastomosis*. He also performed a temporary gastrostomy for feeding purposes.

In a personal case the *Torek operation of exteriorization* was performed.

### Carcinoma of the Esophagus

This is a common malignancy, making up about 6 per cent of all. Usually it is a squamous-cell carcinoma of low malignancy, derived probably from the stratified squamous epithelium of the esophagus. By metaplasia any type of carcinoma may be found. In the cardiac end, adenocarcinomas are frequently seen. These are usually true gastric carcinomas extending up into the esophagus,

but may be derived from misplaced gastric mucosa occasionally seen in the lower esophagus. The lesion typically begins as a flattened elevated area in the mucosa. This may fungate but tends to become ulcerated. It partially encircles the lumen, seldom completely. Fibrosis and growth of the mass decrease the lumen until first partial, then complete, obstruction result.

Spread of the upper carcinomas is first local by continuity and contiguity, then to the regional lymph nodes (cervical or mediastinal). Only rarely do they produce early distant metastases; 25-40 per cent of autopsies in these cases reveal no distant metastases. Local invasion of the larynx, trachea, or bronchus may occur, and then fistula formation is common. It is usually followed by aspiration pneumonia. Ulceration into the aorta or other great vessel may cause sudden exsanguinating hemorrhage. Empyema, mediastinitis, and lung abscess are common causes of death.

Lower esophageal carcinomas act similarly except for location. There is a greater tendency for metastases to occur in the retroperitoneal lymph nodes and the liver. The cardiac gastric adenocarcinomas act like other gastric cancers producing metastases in the nodes of the gastrohepatic omentum and in the liver.

**Etiology**—This is unknown. It is usually seen in men past forty. It may develop on the basis of an old stricture or area of ulcerated mucosa. Drinking of very hot or irritant liquids has been considered a cause by some. Wu and Lucks<sup>124</sup> report that it is very prevalent in North China and is more frequently seen than carcinoma of the stomach. Perhaps its frequency is related in some way to North Chinese eating habits, such as that of eating chicken chopped up into small pieces with the bones included.

**Symptomatology**—The patient, usually a middle-aged or elderly male, complains of progressive difficulty in swallowing of first solid foods, then soft foods, and finally liquids. There may be a burning or deep pain in the substernal region or in the back, usually of a constant type but sometimes similar to that of peptic ulcer. There is usually considerable weight loss due to the inadequate diet.

**Diagnosis**—Visualization of the esophagus by fluoroscopy and x-rays after swallowing barium will usually reveal the lesion or at least evidence of obstruction. Esophagoscopy will visualize the lesion and often permit the obtaining of a biopsy. When it is considered that benign strictures usually have a long history, and that benign tumors (leiomyoma) rarely obstruct, the diagnosis is fairly evident even from the roentgenographic studies. Hill and Vinson<sup>125</sup> have shown that in 50 cases of intrathoracic tumors in close association with, but of extraesophageal origin, only four had symptoms of dysphagia. The elasticity and mobility of the esophagus keep it from being easily obstructed from without except by an encircling lesion.

**Treatment**—Gastrostomy is a valuable palliative for advanced carcinoma of the esophagus. In earlier cases it may be done as the first step in an attempted surgical cure, or for the purpose of visualizing the liver, gastrohepatic omentum, and retroperitoneal nodes for metastases.

**X-ray or radium therapy** may give considerable local palliation, and if no obstruction exists is well worth while in inoperable cases as the only form of treatment. Most of these cases will require *gastrostomy* because of obstruction.

**Surgical resection** of the tumor-bearing portion of the esophagus is not an

uncommon procedure today in well-equipped thoracic surgical clinics. It offers the patient a chance for complete cure, although the number of such cures is not yet great. The reasons are: (a) The late stage of the disease at which these cases are diagnosed (unfortunately, frequently unnecessarily late—considering the frequency of the disease and the early onset of symptoms in many cases), and the even later date at which the cases are referred for surgery; (b) the advanced age or debility of many of these cases. Associated cardiovascular and renal disease are almost the usual picture; dehydration and starvation are common; (c) the ignorance of the laity and even of many physicians that these patients can be offered a chance of cure at a reasonable surgical risk; (d) the technical difficulties associated with reconstruction of the gastrointestinal continuity. These have been considerably overcome by animal experiments and early experiences in clinical cases, but there is still room for further improvement.

Kay<sup>126</sup> has made a very serious study of these problems of reconstruction and has worked out an improved surgical technic on dogs. The main technical obstacles to simple resection of the tumor-bearing segment and direct anastomosis of the cut ends in human cases are: (1) The lack of a serosal coat on the esophagus; (2) the lack of redundancy of the esophagus; (3) meager blood supply of the esophagus; (4) the longitudinal fibers of the muscular coat of the esophagus which tend to pull an anastomosis apart; (5) the esophageal lumen contains very virulent organisms.

He discusses the virtues of direct esophagogastric and esophagojejunal anastomosis in low esophageal lesions as compared to the Torek method of exteriorizing the esophageal ends after re-

section, with the idea of later plastic reestablishment of the alimentary continuity.

In dogs he has performed first an abdominal incision and prepared a long gastric tube from the greater curvature of the stomach with its base 3 to 4 cm. from the cardiac orifice. The diaphragm is opened, the tube is laid in the thorax, and the diaphragm then sutured about it. **Splenectomy** is routinely done. One advantage in human cases would be the opportunity to explore the liver and subdiaphragmatic region for possible metastases. The second stage is performed through the thorax. A portion of esophagus is resected, the lower end is closed by inversion, and a direct anastomosis of the upper end to the gastric tube is performed. In only 3 of 12 cases was there disruption of the anastomosis. In human cases, should the lesion prove inoperable, Kay suggests that the gastric tube may be brought out on the chest wall for a **gastrostomy**, or even that a **palliative operation** be done. It would seem that such operations should only be done on good-risk human subjects.

He has also tried bringing the gastric tube up under the skin of the anterior chest wall for anastomosis to an upper end of the esophagus brought down under the skin antethoracically. He feels the gastric tube is not long enough to be satisfactory for such a procedure. Isolated **jejunal loops anastomosed to the stomach and brought up antethoracically** worked out much better, and this procedure has the further background of having been already used successfully in human cases by Davis and Stafford,<sup>127</sup> and others.

Surgical resection for carcinoma of the esophagus is best considered separately for each of three clinical divisions of the esophagus.

Carcinoma of the cervical portion of the esophagus is probably best treated by first preparing a large rectangular flap of skin and platysma from the anterior and lateral portions of the neck, pedicled on the left side. The esophagus is then dissected up, and the tumor-bearing segment is excised. The larynx should be removed at the same time if it is involved by the growth. In that case the trachea is exteriorized and a tracheotomy tube inserted. The flap of skin and platysma is then dropped into the esophageal bed and anastomosed above and below to the cut ends of esophagus, or esophagus and pharynx. The skin tube is left open anteriorly to avoid tension on the suture lines. Later, a minor plastic operation may be done to repair this defect. The raw surface on the right side of the neck may be allowed to granulate in or may be primarily skin grafted with split thickness grafts. A Levine tube inserted through the nose, through both anastomoses, and into the stomach will suffice for feedings. The mortality of this operation is very low.

Carcinoma of the thoracic esophagus, except very low lesions, had probably better still be treated by the *Torek operation* or one of its modifications. Kidd<sup>128</sup> employs the abdominocervical approach. This permits exploration of the liver, resection of the lymphatics of the lesser curvature of the stomach, and any portion of the stomach. The esophagus is drawn up the mediastinum through the cervical incision. It is essentially a blind operation and would seem very dangerous in view of the trouble and hemorrhage we may have in mobilizing and resecting the esophagus even under direct vision.

Torek, after a preliminary gastrotomy, made a transpleural thoracic incision on the left side, and mobilized the

thoracic esophagus. He divided it below the tumor, and closed the lower end. The upper end he drew up and out of the mediastinum through a cervical incision. He then cut off the tumor-bearing portion and drew the remainder of the esophagus down under the skin of the anterior chest wall as far as possible and then exteriorized it on the skin. The patient lived 14 years and fed herself by ordinary mastication, a rubber tube being used to connect the esophageal end and the gastric opening. Her death was from advanced age.

Santy, Ballivert, and Berard<sup>129</sup> recommend essentially the Torek operation but perform it from the right side because of greater ease in mobilizing the esophagus. The azygos vein is usually divided. They advise a preliminary pneumothorax and thoracoscopy. Ferrari<sup>130</sup> advises a preliminary pneumothorax but prefers the left-sided approach. Allison<sup>131</sup> employs the right-sided approach when the lesion is in the middle of the esophagus. The advantages of the right-sided approach are indeed appreciable when one considers that the right mediastinal pleura is frequently involved early by direct extension. It may easily be resected from the right-sided approach. Also, tumors in the region of the arch of the aorta may be technically unremovable by blind dissection from the left, but easily resected from the right.

Franklin<sup>132</sup> used the right approach. He insists that the tumor be removed before drawing the esophagus out of the neck.

The extrapleural approach would seem preferable to the transpleural approach in certain cases to avoid the danger of empyema.

Garlock has recommended that when the left-sided approach is used, the lower end of the esophagus be brought through

the diaphragm and out upon the abdominal wall as a gastrostomy.

All of these exteriorization operations require that the patient either feed himself through his gastrostomy or jejunostomy or else that a rubber tube be used to connect the upper and lower alimentary openings, at least temporarily. A plastic reconstruction is very desirable. Most of the new tube probably should be made of skin, as it is easily the most available repair tissue. Jejunum has been brought up under the skin as high as the cervical region but this requires an anomalous formation of the mesenteric vascular arches. Usually it is best to use an isolated segment of jejunum to connect the lower end of the skin tube to the stomach, as described by Davis and Stafford.<sup>127</sup> The gastric juices tend to digest an anastomosis of skin to stomach or gastrostomy tube. Garlock mentions this as one of the advantages of using the lower portion of the esophagus for a gastrostomy tube.

For carcinoma of the lower portion of the esophagus, or of the cardia of the stomach, a transthoracic approach through the bed of the resected left ninth rib would seem best. If necessary the incision may be extended down on the abdominal wall, to make an abdominothoracic approach. The stomach and its lymphatic drainage may be widely resected, along with the lower portion of the esophagus. The stump of the stomach may be anastomosed to the esophagus, or if too much stomach has been resected, the jejunum may be brought up in the thorax for esophagojejunal anastomosis. The suture line should be reinforced by available omentum and tension sutures holding the stomach or jejunum to the periosteum of convenient vertebrae or ribs. The diaphragmatic

rent is sutured to the wall of stomach or jejunum after intrathoracic phrenic crush.

### Diaphragmatic Hernia

Harrington<sup>133</sup> has reviewed 295 cases treated surgically. Of these, 253 were congenital and 42 traumatic. Of the congenital, 223 were through the esophageal hiatus with a normal length of esophagus, and 14 were due to a congenitally short esophagus; seven were hernias through the pleuroperitoneal hiatus, four through the foramen of Morgagni, and five through a congenital defect in the posterior quadrant of the left diaphragm. Of the traumatic cases, 41 were left sided and one right sided.

He recommends that before leaving the operating room, an x-ray be taken. If any mediastinal shift is present, it should be immediately relieved.

Dorsey,<sup>134</sup> in describing the surgical treatment of diaphragmatic herniae in children, recommends either a preliminary *phrenic crush operation* or else a subcutaneous placing of the abdominal viscera, as described by Ladd and Gross,<sup>135</sup> at the time of diaphragmatic repair. Otherwise, the increased intra-abdominal pressure will add greatly to the operative mortality. The placing of the viscera subcutaneously requires a later reparative operation, after the abdomen has increased in size.

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## WAR SURGERY

WILLIAM L. MARTIN, COMDR., M.C.V.(G), U.S.N.R.

### GENERAL CONSIDERATIONS

#### Trends in War Surgery

**Basic Features of Treatment**—The basic features of treatment in war injuries may be said to revolve around the following points:

1. *The time element.* The time lag between the onset of injury and definitive treatment is *the* most important element. Moorhead<sup>1</sup> designates it as six hours.
2. *The shock element.* Do not undertake any extensive operative procedures

unless the blood pressure is over 90. When shock and hemorrhage coexist it may not be possible to fulfill this important requisite. 3. *Débridement* is the recognized treatment for any extensive wound; it is recommended that sutures not be used. 4. *Dressings* should be ample, as immobilization is an important

*eign bodies* are removed if accessible. The use of the *Locator* is very helpful. The *sulfa drug element*—after débridement, a sulfa drug is liberally applied to every section of the exposed surface. The *no-suturing element*—the débrided wound is left wide open if it is extensive or comminuted; otherwise, sutures

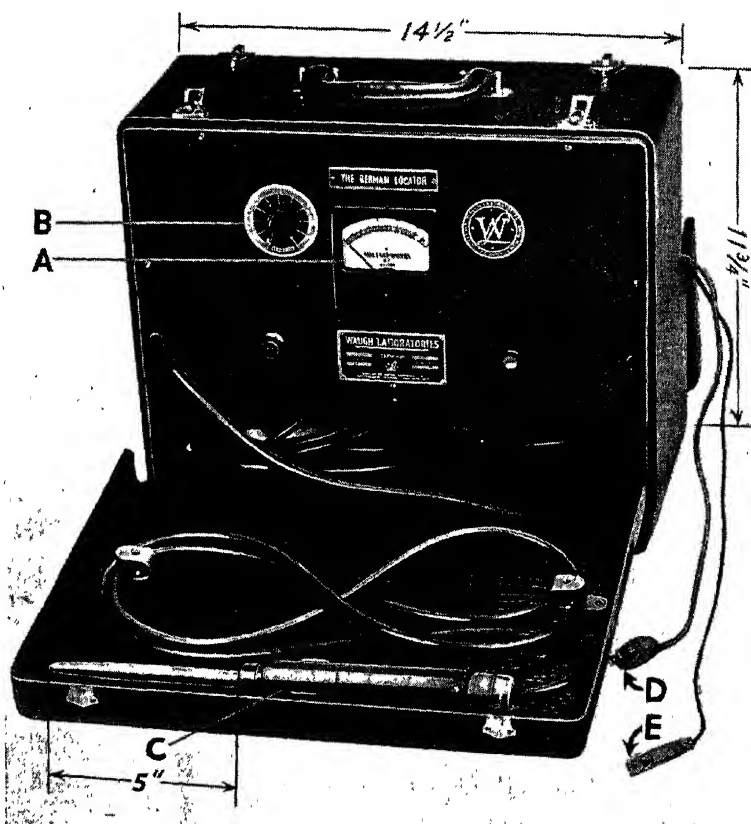


Fig. 1—The Locator foreign-body finder. In size and shape it resembles a portable radio. It responds for iron, steel, copper, brass, aluminum, lead, and other metals. *A*, the registering dial. *B*, the tuning-in knob. *C*, the probe or finder. *D*, the plug-in wire. *E*, the ground wire. (J. J. Moorhead: S. Clin. North America.)

element too often neglected. Defer redressings beyond the third day, as a rule, and at that time take great care to prevent reinfection. 5. *After-care* is often featured by the use of transfusion.

**Wounds**—The *cleansing element* universally advised in wounds is soap and water. The *débridement element* (excising all damaged tissue) is complete when the tissues look normal, the tissues bleed, and the tissues contract (if muscle). *For-*

are placed but left untied until after the third day. The *after-care element*—firm massive gauze dressings with splintage of adjacent joints is advisable.

**Fractures**—These are usually of the grossly compounded variety and for this reason the preceding elements of wound treatment are even more applicable. The delayed suture method applied to soft part wounds was likewise applied to wounds involving bone (fractures).

**Burns**—Here the essential aims are to relieve pain, combat primary and secondary shock, promote healing, and prevent infection and deformity. Healing is promoted by any medium that stimulates the secreting surface and at the same time prevents fluid loss and avoids secondary infection. Immobilization of the burned surface is just as important as in any other type of wounds, with the precaution to enforce mobility in affected joints and in burns of the face or hands and feet.

**Anesthesia**—Anesthesia is very important in war wounds, and accumulating experience commends the intravenous route in preliminary treatment and for long procedures as well. Its smooth induction and recovery prevent the tossing about so disturbing in bleeding wounds and in fractures. It is also very easy to administer.

### War Wounds

**Tissue Destruction and Contamination**—According to Sheehan,<sup>2</sup> two effects are produced at the area of actual contact. The force exerted by the missile may so completely disrupt the tissue with which it comes in contact as to render it incapable of resuscitation; and the area traversed by the missile is contaminated. In the one case, dead tissue is to be cut away; in the other, the wound is to be made clean.

**Traumatic Agencies of War**—In the main, these are bullets, shells, and bombs. Tanks and airplanes, both driven by highly inflammable fuel, giving a greater proportion of burn injuries, are other agents. What is notable about the present war is the multiplicity of wounds that may be received by the same person at the same time.

**Blood Supply**—The difference between early and late attention to wounds lies in the fact that the process of re-

sistance to invasion by bacteria reacts upon the blood supply, reducing the volume either by hemorrhage or by withdrawal from the system of the plasma fluid and the proteins it holds in solution. Restoration of blood volume with normal hemoglobin concentration is essential to save life. This is done best by using *plasma* which restores the protein bearing fluid. It also equips the blood stream to combat effectively the infection which can become so prevalent in contaminated wounds.

### Care of Battle Casualties

Following the Japanese attack on Pearl Harbor, patients were received at the Naval Hospital<sup>3</sup> at the rate of three a minute for three hours. They were distributed to all wards and the main operating suite as they arrived. Approximately 47 per cent of all casualties admitted were cases of burns. With a few exceptions, the remainder were acute surgical emergencies. Upon admission, all patients not known to have been previously morphinized, were given 0.03 Gm. ( $\frac{1}{2}$  gr.) *morphine sulfate* hypodermically, followed by *tetanus anti-toxin*, 1500 units, alone or combined with *anti-gas serum*. Preliminary cleansing of patients was impossible.

A well organized, smoothly running team is important in caring for war wounds efficiently. The first object is to save life by controlling hemorrhage, by allaying shock, and by every possible effort to prevent infection. It is important to label patients conspicuously or mark them on the skin before evacuation to hospital, so that the next person treating them will know when a tourniquet was applied, when morphine was given and dose, etc. When possible, it is best not to remove the patient from the stretcher on which he is placed when first picked up, until he is finally de-

posited in his ward bed. This lessens possible shock. Immediately necessary treatment for shock may easily be given with the patient on a stretcher. Major operations can also be performed with the patient on a stretcher.

If any large number of injured is to be cared for it is important that a special ward or wards be designated for the treatment of shock, that its staff be especially competent to administer such treatment, and that it be adequately equipped with ample apparatus for this purpose. Wards for burned patients should be similarly specially equipped for burn therapy.

The importance of the *Orr-Trueta plaster cast treatment* for extensive wounds of the extremities was emphasized at the Naval Hospital, Pearl Harbor, and in evacuation of patients to the mainland. This treatment very definitely relieves pain and promotes healing. Patients can be transported in comparative comfort while their wounds improve instead of possibly becoming worse. An excellent substitute for a plaster splint in the field is a *papier-maché splint* first adopted by the French and later by the British.

One of the most important lessons learned at Pearl Harbor was the imperative necessity for hospitals or any medical activity in areas subject to enemy air attack to provide themselves with large stocks of reserve medical supplies, sterile gauze, shell dressings, etc., and to scatter these in several of the most widely separated and best protected rooms or spaces available.

A very important detail is to simplify technic as much as possible. The immediate treatment can be only advanced first aid—administration of morphine, treatment of shock, and prevention of infection. Administration of plasma to

severely burned patients must be started with the least possible delay.

**Treatment Aboard Ship**—After an experience with more than 4000 casualties handled with a mortality of 7 patients (0.18 per cent), aboard a hospital ship, Ferguson<sup>4</sup> concludes that *mechanical cleansing, local sulfathiazole, pressure dressing, and immobilization* have proven the most effective method of wound treatment. Wounds of the face and mouth are the exception to the rule against early wound suture. Also, suture of the muscle and fascial layers, only, should be attempted in closure of the abdominal wound, in cases of colon perforation. Conservative treatment should be given to chest wounds and cases of suspected gas gangrene. Secondary hemorrhage is a constant threat for which adequate emergency treatment must be available. Foreign bodies should be removed when they produce infection, when they lie in joints, or when they produce pain or other symptoms by pressing upon or involving vital structures.

In working aboard a light cruiser, Creagh<sup>5</sup> found that early treatment is important. In burns, early supportive treatment, rest, and deferment of local treatment until the patient recovers from primary shock should be emphasized. Compound fractures receive *open reduction, careful but limited débridement, sulfanilamide* locally with *immobilization in plaster cast*. Gunshot wounds, after thorough *irrigation with warm tap water*, received the same type of treatment.

**Treatment on Land**—In reporting on casualties from the initial Solomon Islands engagement, Crile<sup>6</sup> found that they were of three main types: Gunshot wounds received during landing operations and on the beaches; wounds re-

ceived aboard ship as a result of shell fire, and burns received aboard ship. The various types of injuries occurring in these cases are listed in Table I below.

Subsequent experience with casualties received from the same area has been along the same lines. Incidence of wounds

zation for the evacuation of wounded is their central administration of medical services, directed by the chiefs of the given army, not the individual division. A further aid to quick evacuation is the organization of Women Medical Orderlies, who operate in the line of fire and

TABLE I.  
TYPES OF INJURIES.

Diagnosis	No. of Cases	Per cent	Diagnosis	No. of Cases
Flesh wound.....	114	..	Injury of tendon.....	6
Clean.....	..	88	Fractured jaw.....	6
Infected*.....	..	12	Simple fracture.....	6
Compound fracture.....	104	..	False aneurysm (arterial hema-	
Clean.....	..	86	toma).....	5
Infected*.....	..	14	Concussion.....	4
Burns, second degree.....	40	..	Fractured skull.....	4
Clean.....	..	83	Perforating wound of abdomen....	4
Infected*.....	..	17	Neurosis (developing after the	
Burn, third degree.....	6	..	engagement).....	3
Clean.....	..	0	Deafness (marked, bilateral).....	2**
Infected*.....	..	100	Injury spinal cord.....	2
Injury of peripheral nerve.....	30	..	Contusion.....	1
Injury to eye.....	18			
Amputation (traumatic or surgical)..	11		Total.....	383
Penetrating wound of chest.....	10			
Soft tissue defect requiring plastic			Deaths.....	1
operation.....	7			

\* In this survey a wound was not considered to be infected unless cellulitis, a systemic reaction, or a profuse purulent discharge was present. Wounds showing smaller amounts of purulent or sero-purulent discharge were not listed as infected.

\*\* 10 partial.

(G. Crile, Jr.: U. S. Nav. M. Bull.)

of the abdomen and wounds of the head has remained lower than expected. Chief problems are the treatment of infection and the covering of denuded areas with skin. *Pentothal* anesthesia proved safe, adequate, and satisfactory for minor surgical procedures. There has been little use for plasma, as cases have been well beyond the critical phase of shock. *Citrated blood* was widely used in treating hemorrhage and anemia. The most striking feature of these casualties has been the rapidity of recovery.

Elman<sup>7</sup> reports that one of the outstanding features of the Russian organi-

alone bring wounded soldiers back to the field dressing station, after administering the simplest of first aid care. As in our services, the Russians emphasize the three problems of shock, infection, and delay in definitive therapy. Many burns are now being covered with a layer of pine sawdust and then bandaged. This material is being used because it is plentiful, and because it seems to exert an absorptive, cushioning, and antiseptic effect. Blood and plasma are used extensively in treating shock, but much more whole blood is used, preservation being achieved by the addition of dextrose.

Whole blood of the universal group is also employed widely.

Russian figures on the results of treatment show a mortality of only 1.5 per cent; of the wounded who recovered, 70 per cent have already been returned to the ranks and 10 per cent are still undergoing treatment and are expected to be returned to service very soon. Having had long experience with ambulance planes, the Russians have made use of them not only in evacuation of the wounded, but also in removing wounded from besieged cities.

Johnston<sup>8</sup> joins in the general opinion that the cardinal principles of treating burns are control of pain, replacement of fluid loss, prevention and combating of shock, and treatment of all burns as open wounds. The great aids in case of combat wounds are *morphine*, *sulfonamides*, *plasma*, and *immobilization*. Conservative measures should always be used, except in certain wounds of the abdomen.

### Blood and Blood Substitutes

**Indications for Use**—Schaefer<sup>9</sup> emphasizes the importance of following a rational plan in using blood and blood substitutes in surgery. The requirements and characteristics of the individual patient must be considered in order to obtain the most beneficial results. A knowledge of the advantages and limitations of the various kinds of fluids used intravenously is essential for their judicious use. Treatment for shock should be instituted before the classical clinical picture is manifest. Changes in the blood volume and hematocrit reading are indicative of impending shock. *Whole blood* is the ideal replacement for hemorrhage; however, *plasma* is extremely useful as interval therapy until whole blood can be obtained. In the replacement of fluid lost by the body, the best results are obtained when an

equal amount of the same fluid is used. The routine use of *physiological saline* should be avoided except when specifically indicated, since it may produce or aggravate tissue edema.

**Dicoumarin and Prophylactic Anticoagulants:** The anticoagulant property of dicoumarin forms the basis of its therapeutic significance. Observations and experimental studies at first strongly suggest the value of its administration in preventing intravascular thrombosis. Like other anticoagulants, it possesses certain hazardous features.<sup>10</sup> Of these, the most important is hemorrhage, which in surgical cases obviously assumes even greater significance. In renal insufficiency, or cases with an already prolonged prothrombin time, such as obstructive jaundice or other vitamin K deficiency diseases, the drug should be employed cautiously or not at all. The unexplained variations in the prothrombin and hemorrhagic response to dicoumarin in different individuals emphasize the significance of this fact. In view of the present lack of trenchant knowledge concerning the etiologic factors in intravascular thrombosis, the rationale of anticoagulants as combative measures may be justifiably questioned.

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## THE ABDOMEN

### The Spleen

**Traumatic Rupture**—This injury may be classified under the following six headings; as indicated by Harkins and Zabinski.<sup>11</sup>

1. Spontaneous rupture of the normal spleen.
2. Spontaneous rupture of the diseased spleen.
3. Traumatic rupture of the normal spleen.
4. Delayed rupture of the normal spleen.
5. Delayed rupture of the diseased spleen.
6. Traumatic rupture of the diseased spleen.

From the practical standpoint, types 3 and 4 are by all odds the most im-



portant. Of 10 cases, 5 are classified as Type 3, 4 as Type 4, and 1 as Type 6. Immediate *splenectomy* is the ideal mode of treatment. For delayed traumatic rupture, a similar therapy is essential, but almost as important is the realization that such a syndrome does occur. Traumatic rupture of the spleen of all types is the most frequent serious subcutaneous abdominal injury. At least one-seventh of all splenic ruptures are of the delayed type.

### Abdominal War Wounds

**Traumatic Wounds of the Abdomen** — Abdominal injuries are usually serious. According to Glenn and Moore,<sup>12</sup> they may be divided roughly into penetrating and nonpenetrating wounds and intra-abdominal trauma without visible wounds of the abdominal wall. All penetrating and nonpenetrating wounds require surgical exploration and débridement. All penetrating wounds require in addition careful systematic inspection of all viscera and the performance of the least possible surgical procedure compatible with saving life. Patients with intraabdominal trauma without visible wounds of the abdominal wall often require a period of observation for diagnosis and may or may not require operation.

Shock and hemorrhage commonly accompany all three types of wounds and may be adequately treated by various measures, but there remain the even greater problems of infection and postoperative complications. For the former recently developed *chemotherapy* has proved valuable. For the latter there remains unrelenting and meticulous postoperative care, which includes the maintenance of blood constituents in proper amounts and fluid balance, the prevention of intestinal stasis and obstruction, as well as the early recognition of the

causes of elevated temperature such as intraperitoneal abscesses and wound infection.

Patients with abdominal wounds are invariably in a rather marked degree of shock when first seen, according to Heaton.<sup>13</sup> Prompt relief, especially by the use of *plasma*, aided by *blood transfusion* and *saline and glucose infusions*, is indicated, before operation.

**Technic**—As a rule, either a midline or a right paramedian incision has been used, through clean untraumatized tissue if at all possible. Adequate exposure is a fundamental principal. Open drop *ether anesthesia* is superior to all others in these cases. After being satisfied that no gross hemorrhage exists, the bowel is examined in a definite and systematic fashion. Colon damage is repaired before examining other organs, followed by the same treatment of the small bowel and its mesentery. Injury to the duodenum is rare, but stomach perforations are frequently found.

The next step is examination of the solid viscera, bladder and retroperitoneal structures. Removal of the spleen, if torn, is preferable. Large liver tears respond well to packing with gauze and sutures, tied over a free edge of omentum, are employed in smaller ones. Gallbladder and duct damage receive temporary drainage, as do pancreatic wounds, which are self limited. Bladder tears require simple suturing and indwelling catheters. Rectal wounds should be treated by packing of the retrorectal space or by suture and colostomy.

In any gastrointestinal wound, suture of perforations in the transverse direction, rather than resection, should be practiced whenever possible. Holes in the free portions of the colon may be closed by purse string or invaginating sutures, if surrounding bowel wall ap-

pears healthy, but in many cases resection is advisable. End-to-end technic is used whenever possible. All of these closures are done with gut and silk, employing the Connel, Cushing, or Lembert stitches.

In all abdominal wounds from 4 to 16 Gm. (60 to 240 gr.) of powdered *sulfanilamide* have been placed intraperitoneally and over the suture lines at the completion of surgery. Drains or packs are brought to the exterior through stab wounds or through entrance or exit wounds after débridement, if in a suitable position. The exploratory wound is closed tightly in layers and as a last resort any remote entrance and exit wounds are débrided. *Sulfanilamide powder* and *vaseline gauze* are then inserted in the resultant tracts.

**Postoperative Routine**—Parenteral fluids and morphine are given as required. Ileus is combated with *continuous Wangensteen suction* or *Miller-Abbot tubes*. *Oxygen tents or masks* are of considerable help in most cases. After the first 24 hours, when adequate blood levels are maintained from peritoneal absorption, *sulfonamide therapy* is used for several days as a prophylactic measure in all cases. *Sodium sulfadiazine* intravenously, particularly when oral administration is impractical, was found to be far superior to other sulfa drugs. Oral dosages have averaged 1 Gm. (15 gr.) each four hours, maintained from three to seven days. A urinary output of at least 1000 cc. per day is essential when patients are on such therapy. *Blood transfusions* and other supportive measures are given as indicated.

**Perforating Gunshot and Stab Wounds**—Hamilton and Duncan<sup>14</sup> have reviewed a series of 190 perforating gunshot and 146 perforating stab wounds

of the abdomen. The mortality for the entire series was 51 per cent for the bullet wounds and 14.1 per cent for the stab wounds. The operative mortality was 48.9 and 13.8 per cent, respectively. They observed a greater incidence of vomiting, pain, spasm, and tenderness in penetrating wounds, with visceral trauma, although many do not show significant symptoms and signs, and, contrariwise, these same signs and symptoms are frequently present in cases with no penetration. In gunshot wounds, 56.7 per cent of the deaths were caused by shock and hemorrhage, while the other greatest single cause of death was peritonitis. The authors particularly emphasize the value of peritoneoscopy in diagnosing peritoneal perforation in doubtful cases. Hemorrhage is synonymous with shock in perforating abdominal trauma and, therefore, operation to control it brooks no delay. Abdominothoracic injury is more serious than generally realized and amenable chest injuries are too frequently overlooked or inadequately treated. *Autotransfusion*, regardless of blood contamination, is urged for all seriously injured patients operated upon within six hours.

**Chemotherapy**—The management of victims of penetrating abdominal gunshot wounds comprises the treatment of hemorrhage and shock, and the treatment of peritonitis. In a group of 100 such cases, Loria<sup>15</sup> reports that 49 received some form of chemotherapy, whereas 51 were more or less similarly handled except that no sulfonamides were used as additional treatment. In the first group, the mortality rate was 18.4 per cent; in the second, 50.9 per cent. Eleven patients getting intraperitoneal implantations of *sulfathiazole* and showing no deaths were especially interesting. No patients treated with the *sulfonamides* showed any evidence of toxicity. It ap-

pears that the sulfonamides are especially beneficial in those cases showing "massive" hemorrhage. Such cases showed a 91.6 per cent mortality as compared to the 40 per cent fatality in the group receiving chemotherapy.

**Intraabdominal Injuries**—Of the 115 cases of intraabdominal injuries reported by DiLorenzo *et al.*<sup>16</sup> abdominal signs and symptoms were present in all but 10. These signs and symptoms may be masked by shock and alcoholism; of the 10 asymptomatic patients, five were in severe shock on admission. All patients, the authors conclude, should be operated upon at the earliest possible moment consistent with the adequate preparation of the patient and the adequate treatment of shock. All cases must be thoroughly explored through adequate incisions and the importance of transfusions of citrated whole blood and plasma is stressed. Sulfonamides intraperitoneally and intravenously are indicated in all cases in which the peritoneum is contaminated from within or without. All patients with gastrointestinal perforation should be treated as cases of potential peritonitis, receiving Ochsnerization, blood, and sulfonamides.

**Nonpenetrating Abdominal Trauma**—Kelly<sup>17</sup> reviews the incidence and mortality rate of nonpenetrating abdominal trauma, covering a period of 15 years in a general hospital. In this period 74 cases were admitted, which makes a small incidence and a very high mortality rate, as is shown in Table II. Most of the doctors saw very few patients with this type of injury and there was no uniformity of treatment. However, it is concluded that mortality should be lessened by proper training of first-aid workers, internes in accident rooms and wards, and doctors; use of plasma in shock; operation within six hours if

indicated, and proper use of the sulfa drugs intraperitoneally.

**Postoperative Foreign Bodies in the Abdomen**—In many cases the presence of an intraabdominal foreign body, following surgery, can be suspected when a patient does not recover from his op-

TABLE II.  
TYPE OF LESION.\*

	Total	Died	Recovered	Died (Per cent)
Bladder . . .	55	3	2	60
Intestine . . .	12	9	4	69
Kidney . . . .	29	3	26	10
Liver . . . . .	16	12	4	75
Mesentery . .	1	0	1	0
Spleen . . . . .	9	5	4	55
Stomach . . . .	1	1	0	100
Total . . . .	74	33	41	44

\* E. C. Kelly: Surgery.

eration as rapidly as expected, according to the findings of Guzzetta.<sup>18</sup> The presence of obscure abdominal pains, and frequently nausea and vomiting, during convalescence, should always arouse suspicion if these untoward symptoms are not easily explainable. The symptoms depend upon whether the foreign body is septic or aseptic. If septic, peritonitis is the usual result, with very frequently a fatal outcome; however, in the case of aseptic foreign bodies there is a strong tendency for encapsulation, with acute symptoms appearing after variable periods of time. Rarely, no symptoms whatsoever are produced. Frequently, abdominal foreign bodies are extruded into the lumen of a viscus, usually the bowel or bladder. This is a serious complication, but not necessarily fatal. There is also a tendency for foreign bodies in the abdomen to erode the surrounding viscera.

**Precautions**—A considerable number of precautions should be taken, in an attempt to prevent the type of case which is under consideration. First in importance, probably, is an assurance by the surgeon that all sponges and instruments are accounted for at the close of each operation. Small sponges should be cleared from the operative field just before the peritoneum is opened in abdominal surgery, and thereafter only large laparotomy sponges with metal rings attached should be used. An x-ray examination will then determine the presence of a sponge if there is any suspicion post-operatively. The use of Corssen's "saddlebag" arrangement has also been recommended, as has the use of a metal rod sponge carrier to which all sponges are attached by a long tape and metal ring. As the sponges are used they can be moved out of the surgical field. All instruments should also be checked regularly for loose parts, as a considerable percentage of foreign bodies are screws and other small parts of instruments. Finally, but of considerable importance, is the use of uniform methods in assistance and operative technic.

## ANALGESIA

### Intravenous Use of Morphine Sulfate

The intravenous use of morphine sulfate is advocated in certain cases because the desired full analgesic effect is obtained immediately from an accurately regulated and individualized dose of the drug.<sup>19</sup>

**Administration**—Ampules of a sterile solution of morphine sulfate are preferable, but the tablet form may be used. A 1 cc. ampule containing 10 to 15 mg. ( $\frac{1}{6}$  to  $\frac{1}{4}$  gr.) of morphine sulfate is aspirated into a 2 cc. syringe. A No. 20 gauge intravenous needle is attached. After venipuncture 1 cc. of blood is

drawn into the syringe, and the syringe rotated gently to facilitate an even distribution of the blood in the solution. Three-tenths of a cubic centimeter of the resulting solution is administered and one-half minute allowed to elapse. Any idiosyncrasy to the drug will be noted by that time if it is going to appear. The solution is then injected slowly (roughly 0.2 cc. every five seconds) until the desired effect is obtained. No more of the drug should be injected than the amount necessary to obtain the desired result. Eight milligrams ( $\frac{1}{8}$  gr.) may be given hypodermically, if needed, to maintain the effect. It is not considered safe to give more than 15 mg. ( $\frac{1}{4}$  gr.) at any one time. It is safe, after an interval of ten minutes, to give a further injection, 8 to 10 mg. ( $\frac{1}{8}$  to  $\frac{1}{6}$  gr.) slowly until relief is experienced.

## BLAST INJURIES

There are three fundamental determinants in the causation of trauma by blast, namely, the nature of the explosive force; the medium through which the force is transmitted, and the distance from the explosion. The nature of the explosive force embodies the factor of *brisanse*. Velocity or rapidity of the detonation is the main factor determining the brisanse of an explosive system. The distance factor has an important bearing upon the situation in that explosives of a lower brisant character are relatively more effective through the water and for a longer distance.<sup>20</sup>

### Air Blast Injuries

**Head**—More frequently than not there is a mixture of both psychogenic and organic elements, but usually the preponderance of symptoms will point to one of these as the paramount disability. Cases with the psychogenic syndrome

suffer from a combination of the effects of fatigue, fear, and the stress and strain upon the nervous and somatic systems incident to the rigors of war. Patients with organic brain injury are being treated, with gratifying results, by *bilateral trephine* and the *withdrawal of subdural fluid*.

**Chest**—The etiologic factor in blast injury to the thoracic organs is the direct squeeze of the positive component of the blast wave. Carbon monoxide poisoning may be a contributory or solely responsible factor. Shock out of proportion to the apparent trauma is almost always striking, as are respiratory difficulty, cyanosis, pallor, cough, and restlessness. Pain in the chest, more often lateral than central, is a fairly constant symptom. Cough productive of a frothy, blood-tinged sputum not always immediate in development, is paroxysmal and frequently intractable in character. The patient is almost always apprehensive and may be extremely restless. The physical signs referable especially to the chest consist of a restricted respiratory excursion. X-ray findings are fairly typical and frequently simulate a disseminated pneumonia with ill defined or mottled areas of increased density. The bases rather than the apices are more prone to show abnormal roentgenological findings. Hemorrhagic areas in the lung, diffuse due to capillary bleeding into the alveolar spaces or massive in the hilar regions, are found at autopsy.

**Treatment**—*Bed rest* is foremost in importance and for its effectiveness early recognition of pulmonary blast injury is mandatory. For shock the usual measures are applicable save that *intravenous fluids* must be given cautiously. *Blood plasma* is, early at least, preferable to whole blood. For cough, pain, and restlessness, there is nothing better than

*morphine*. *Codeine* may be used effectively if cough alone is the chief annoyance. Give *fluids*, particularly hot fluids, freely by mouth. Next to absolute bed rest the most helpful measure that can be instituted is *oxygen therapy*. It may well be life saving and should be administered at the rate of 8 to 12 liters per minute either by tent, B.L.B. mask, or nasal tube. As pneumonia is a common complication, all serious cases, if not all cases, should receive *sulfa drug therapy*. *Sulfadiazine* in amounts sufficient to maintain a concentration of 15 mg. per 100 cc. of blood is recommended by the best authorities.

### Water Blast Injuries

In a symposium on this subject, covering 35 cases admitted to hospital five days after the injury occurred. Palma and Udall<sup>21</sup> found that there was no external evidence of injury. Distance from the source of the detonation of high explosive and the position of the individual in the water were obviously factors of major importance in the type and severity of injury produced.

Of the 35 cases, 16 were ambulatory with little in the way of complaints but many had roentgenographic evidence of blast injury at the bases of both lungs; one had a transient psychogenic change, and four presented physical and roentgenographic findings comparable to atmospheric blast injury. Of the remaining 14 who presented signs and symptoms of severe abdominal injury, six recovered completely without operation; two recovered with surgical intervention; two recovered after necessary surgical procedures; four died.

**Pathology**—In the four cases coming to autopsy, contrary to air blast injury, the predominating and urgent pathology was abdominal, although there were pulmonary lesions.<sup>22</sup> Mucosa, submucosa,

muscularis, and serosa had been fragmented and perforated. The opposing edges were heavily infiltrated with leukocytes, lymphocytes, and plasma cells, with considerable superficial necrosis. Adjacent serosa had heavy deposits of exudate. Comparatively little regenerative cell growth, fibroblastic activity, capillary extension, or evidences of repair were to be noted around the perforations. The smooth muscle fragmentation was striking. Several findings were noted: The severe intraabdominal trauma in each instance without external evidences of injury; the tendency for the ileocecal region to sustain the severest damage; the "blown out" character of the perforations; the extent of the peritonitis, and the attempts at walling off exhibited in those cases having this reaction. The absence of rupture of the liver, spleen, kidneys, or bladder in each instance is remarkable, as was the fact that in no autopsy was mesenteric thrombosis with subsequent divitalization of gut segment demonstrated.

**Roentgen Findings**—The x-ray findings in the chests of all and in the abdomens of 12 of these 35 patients are reported by Gates.<sup>23</sup> Although all the patients had symptoms referable mainly to the abdomen, 30 or 86 per cent showed abnormal densities in one or both lungs. There was some degree of gaseous distention of the small intestine in all cases and four cases showed evidence of perforation of the intestinal tract. Rather large, soft tissue densities, presumably due to accumulations of fluid, were seen in four cases. Gastrointestinal studies by barium meal in five recovered cases showed a definite abnormality in the mucosal pattern and walls of the small intestine in one case. A fecal fistula originating at the hepatic flexure was seen in one case.

**Neurological Observations**—These cases demonstrate that the nervous system, although less vulnerable than the abdomen or chest to underwater explosion, is liable to a relative degree of injury which should always be looked for by clinical examination and lumbar puncture.<sup>24</sup> Pertinent findings on the cases observed neurologically are summarized in Table III.

**Treatment**—Treatment is predominantly conservative in the majority of cases.<sup>25</sup> Counteract shock; maintain adequate intake of *fluids, colloids, and electrolytes* with infusions of *plasma*, and *glucose* and *saline solution*; interdict all medication, water, and nourishment by mouth; give *morphine* for pain and restlessness; reduce intraintestinal pressure by *continuous Wangensteen suction*, preferably with a *Miller-Abbott tube*; administer *sulfa drugs* intravenously; supply *oxygen* generously; use *whole blood transfusions* if the patient is anemic or shows evidence of intraabdominal hemorrhage; attend to *vitamin requirements*.

**Surgery**—Operation should not be advised unless there is a definite indication. Do not operate if the patient is seen several days after perforation and is in the valley of the shadow of death from general peritonitis. Recent perforation, gangrene of a segment of bowel, and abscess formation demand surgical intervention. Actual surgery was instituted upon only two patients in this series.<sup>26</sup> These patients are poor operative risks and the least, the simplest, and the most expeditious is the safest and best technic. In the first case (intestinal obstruction) *exteriorization resection* and *secondary anastomosis* with the Murphy button was done. The other case developed an abscess in the region of the gallbladder, which was aspirated.

The wound was closed lightly and within a few days a fecal fistula became established, which was closed by surgical intervention later.

**Prevention**—The anterior chest and the entire abdomen should be protected by a lifejacket made of kapok or some

chest injuries, they find, are: (a) The *restoration of normal cardiorespiratory physiology*; (b) the *treatment of shock*, and (c) the *treatment of any complications* or sequelae which may arise. Treatment in general is conservative and nonoperative. **Aspiration**

TABLE III.\*

	Un-conscious	Life jacket	Pulmonary changes by x-ray	Abdominal signs	Neuro-psychiatric abnormalities	Lumbar puncture				Other findings
						Days after immersion blast	Pressure	Cell (R.B.C.)	Total protein	
Case 7	(?)	Yes	Negative	No	Transient disorientation; somnolence	4	135-4-125	2200	40	
Case 8	No	Yes	Diffuse	Yes	No	6	150-5-150	550	40	
Case 9	Yes	Yes	RLL	Yes	No	6	150-5-145	490	45	
Case 2	No	Yes	?RLL	Yes	No	12	120-5-115	0	20	
Case 5	Yes	Yes	LLL	Yes	No	12	180-8-160	8	20	
Case 3	Yes	Yes	Negative	Yes	No	12	150-5-140	2	25	
Case 4	No	Yes	Moderately diffuse	Yes	No	12	180-6-140	5	20	
Case 11	No	Yes	RLL-LLL	Yes	No	12	175-7-160	2	40	
Case 10	No	Yes	Mild RLL	Yes	No	12	155-5-145	2	50	
Case 14	Yes	Yes	Negative 17 days after blast had hemoptysis	Yes	Hyperacusis; hearing loss; involuntary movement	18	190	4 Type unstated	30	Severe residual neuro-psychiatric disorder
Case 13	(?)	No	RLL-LLL	Yes	Personality change	No tap				Fractured transverse processes L 1-4 and body L-2
Case 20	Yes	Yes	RLL-LLL	Yes		No tap				Subdural hematoma; left temporal at autopsy

\* H. Hamlin: U. S. Nav. M. Bull.

other buoyant material.<sup>25</sup> Men should be instructed to swim on their backs if the abdomen is not adequately protected.

### The Thorax

**Treatment**—Elkin and Cooper<sup>27</sup> present a review of 1132 cases of penetrating wounds of the chest, with a mortality of 6.36 per cent and with a 1.76 per cent incidence of empyema. The principal considerations in the treatment of all

*of blood with air replacement* is indicated in case of dyspnea, severe pain, or delayed absorption of blood. In a group of 100 consecutive patients, 89 per cent showed no x-ray evidence of pulmonary lesions after 29 days (average 17 days); 98 per cent had no evidence of pleural thickening at the end of five months.

Bohrer and Lester<sup>28</sup> emphasize that an understanding of the physics and



physiology of the thorax and its contents is essential for the proper treatment of thoracic wounds. The simplest procedure should be employed which will meet the requirements of the pathological physiology. If simple methods are not adequate, the surgeon should not hesitate to use radical procedures. All procedures should be based on accepted surgical principles.

## BURNS

### General Treatment

According to Sheehan,<sup>29</sup> experience gained in treatment of burns under stress of war conditions comes down to this: Plasma and the sulfa compounds have completely replaced the tannic acid-silver treatment of burns, and the long delay incidental to that treatment has been replaced by skin grafting of all burn wounds within five or six weeks of the injury.

Relief of pain both during débridement and at other times should be attained by adequate doses of *morphine* given subcutaneously or intravenously.<sup>30</sup> Control of hemoconcentration and burn shock requires vigorous *plasma substitution therapy* during the exudative phase of from 48 to 96 hours. Given a severe burn involving 20 per cent or more of the body surface, it is well to administer rapidly by vein an initial 500 cc. of plasma for each 10 per cent of involved body surface. Vigorous application of *heat* to patients already on the verge of shock is to be condemned; the temperature should not exceed 80° F.

**Diet**—Depletion and anemia become a serious problem in extensive third degree burns during the sloughing stage and until skin grafting is completed. A high caloric intake should be striven for by a resourceful dietitian. The diet consists of 400 Gm. of carbohydrate, 125 Gm. of protein, and 75 Gm. of fat, total-

ing 2775 calories. The following *vitamin intake* should be assured: 10,000 to 15,000 international units of vitamin A, 2 to 5 mg. of vitamin B<sub>1</sub>, 3 to 5 mg. of vitamin B<sub>6</sub>, 30 to 50 mg. of nicotinic acid, and 75 to 100 mg. of vitamin C. If tolerated, *ferrous iron* should be supplied for hemoglobin regeneration. Almost inevitably it will be necessary, in extensively burned soldiers, to supplement the above with *parenteral protein alimentation*; this can be supplied in the form of a solution of *hydrolysate of casein*. Ravdin<sup>31</sup> never uses *whole blood* in the treatment of anemia for the first few days, unless the anemia is *severe*.

**Infection**—There is increasing evidence that adequate oral intake with the blood level in the vicinity of 10 mg. per 100 cc. is a more effective manner of combating wound infection than local application of *sulfa drugs*. A dose of 4 Gm. (60 gr.), preferably of *sulfadiazine*, should be administered initially. Then, until diuresis is again established, 0.5 Gm. (8 gr.) doses should be given at four-hour intervals; thereafter, the dosage should be increased to 1 Gm. (15 gr.) doses every four hours for as long as considered necessary. Prophylaxis against tetanus should be carried out in all but the most superficial burns by the customary injection of 1 cc. of *tetanus toxoid*.

In addition to the general principles outlined above, Harkins<sup>32</sup> lays emphasis on prophylactic measures, including cleanliness and aseptic local care. He also calls attention to the necessity for *repeated* observation of the blood concentration in severe burns: Every two hours the first 12 hours; every four hours the second 12 hours, and every six hours the third 12 hours. In each instance the indicated amount of plasma should be given.

**Pressure Dressings**—Harkins agrees with Owens<sup>33</sup> that by the use of pressure dressings in the treatment of burns and infected wounds the incidence of

fers comfort to the patient during the first 18 to 21 days because of evenly distributed pressure and its splinting effect.

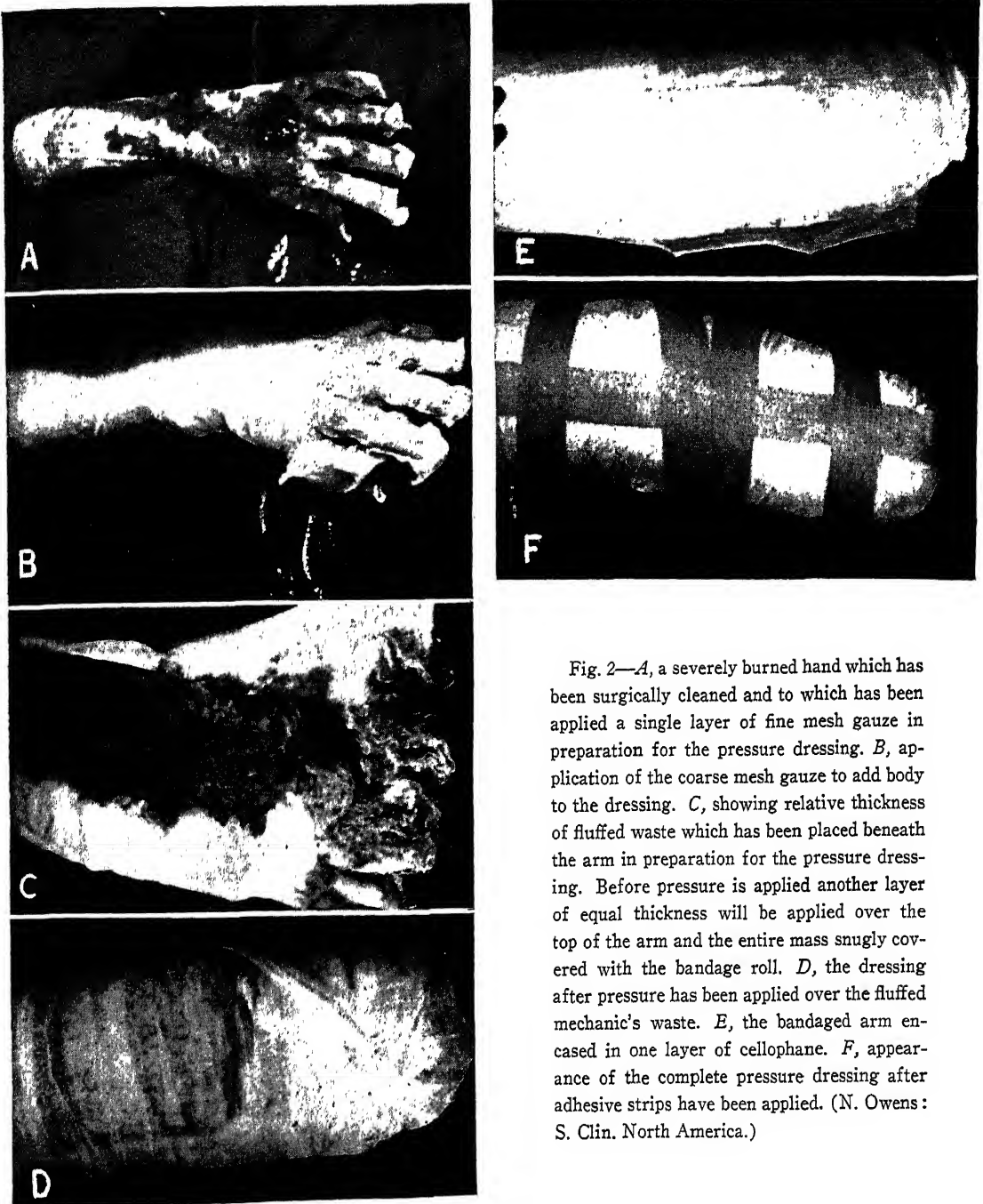


Fig. 2—A, a severely burned hand which has been surgically cleaned and to which has been applied a single layer of fine mesh gauze in preparation for the pressure dressing. B, application of the coarse mesh gauze to add body to the dressing. C, showing relative thickness of fluffed waste which has been placed beneath the arm in preparation for the pressure dressing. Before pressure is applied another layer of equal thickness will be applied over the top of the arm and the entire mass snugly covered with the bandage roll. D, the dressing after pressure has been applied over the fluffed mechanic's waste. E, the bandaged arm encased in one layer of cellophane. F, appearance of the complete pressure dressing after adhesive strips have been applied. (N. Owens: S. Clin. North America.)

complications due to infection has been lowered, the duration of hospitalization shortened, and the complications reduced. A properly applied pressure dressing of-

**Uninfected Burns**—The first step is to cover the entire burned surface with one single layer of fine mesh gauze (No. 44) moistened with normal saline solution

only; over this should be placed a layer of coarse mesh, dry gauze about  $\frac{1}{2}$  to  $\frac{3}{4}$  inch in thickness to give body. These two layers then are wrapped snugly in preparation for applying adequate pressure. Following this, a layer of sterile fluffed mechanic's waste, about six inches in thickness, is placed around the entire area to be enclosed, which is then firmly fixed by a roll of bandage varying from three to six inches in width. Firm pressure should be applied so that the thickness of the mechanic's waste is reduced from six to approximately  $3\frac{1}{2}$  inches. When extreme pressure is applied, the bandage should never be reversed. Following this, one layer of waterproof cellophane of sufficient size to permit an overlap of the pressure dressing at either end should be applied over the entire dressing, snugly fixed with a roll of bandage, and followed by the application of a final layer of three-inch adhesive strips, thus applying additional pressure.

**Infected Burns**—The identical technic described above should be followed, with these additions: A formed dressing should be applied (made in one unit), which is designed to incorporate varying numbers of Dakin's tubes between the layers of gauze forming the dressing. The ends of the tubes, which extend beyond the margin of the dressing, should be connected to a glass tube with multiple outlets. The large open end of this glass unit should then be connected to a rubber tube which is attached to an infusion bottle. **Sterile normal saline solution** or **2 per cent boric acid solution** should be run from the bottle held above the level of the patient through the connecting into the incorporated dressing, in an amount sufficient to give the patient a sensation of moisture. By this technic one can establish sufficient moisture to convert the composite dressing into a

capillary unit establishing drainage from the wound up into the substance of the dressing itself. These dressings should be changed every two to three days and at each change the patient should be adequately protected against potential contamination.

**Emergency Treatment of Extensive Burns**—For emergency purposes, Berkow<sup>34</sup> calls an extensive burn one which cannot be covered by the patient's hand. His plan of emergency treatment is organized in three time periods: (1) On admission, treatment is directed to immediate dangers: Pain, respiratory distress, and continuing injury from magnesium, metal, or phosphorus. Locally, a nonadherent protective covering is applied. (2) If the patient cannot be transferred to a hospital on completion of the primary treatment, a fixed amount of blood plasma is injected. Supportive treatment, to retard and minimize impending shock, is included in this period. The patient receives no further local therapy at this time. (3) When emergency care must be of still longer duration, plasma requirements are estimated and adequate dosage provided. Burned surfaces are guarded against and treated for contamination and further local fluid loss. The danger of the development of subsequent infection is further combated by oral sulfonamide therapy.

**Late Treatment of Burns**—Strange and Mourot<sup>35</sup> believe that burn casualties are best treated on a special "burn" ward with specially trained personnel in attendance. One general surgeon, one plastic surgeon, a physiotherapist, and a laboratory technician should be assigned to each such ward. A dressing of 6 per cent **sulfanilamide** in equal quantities of cold cream and lanolin on No. 44 mesh gauze and compression maintained with elastic bandages fulfills all of the objectives of a burn dressing. The use

of *tannic acid preparations* should be strictly prohibited on the face, hands, feet, and genitalia. Their use on other parts of the body should be permitted only when strict supervision is possible. Early joint movement is superior to splinting. *Skin grafting* should be done as soon as possible—10 to 14 days after the initial injury.

**Protein Nutrition**—Taylor *et al.*<sup>36</sup> report a case with 55 per cent of the body surface burned. Correction of calculable nitrogen deficits, based upon intake and output studies alone, by *high protein feeding* failed to bring the patient into true nitrogen balance because of incalculable losses which were probably from the burned and granulating surface. Heroic *intravenous and tube feeding* apparently restored the true protein balance. This feeding reached a level of intake of the equivalent of 2000 Gm. of protein per week, and resulted in establishment of an apparent positive nitrogen balance of over 6000 Gm. In spite of this apparent positive nitrogen balance, the patient is still more than one-third below normal weight, so that even the calculation and considered deficits are much below the actual level.

**Liver Necrosis** — Hartman and Romaine<sup>37</sup> report on experimental studies of liver necrosis as the result of burns. Large burns result in marked engorgement of the sinusoids of the liver and compression of the liver cells about the central veins. With longer survival, especially if infection either in the form of pneumonia or suppuration of the burned area occurs, actual necrosis of liver cells at the center of the lobule, with myelinization, may be seen. Introduction of *tannic acid*, *ferric chloride*, or *silver nitrate*, either as a dressing or as a subcutaneous injection, increased the incidence of degeneration and necrosis, with

or without hemorrhage. Of these, tannic acid seemed to be the most toxic. Forbes and Evans<sup>38</sup> confirm the hepatotoxic action of subcutaneous acid injections.

### Local Treatment

No matter what method is chosen, the application of sound surgical principles and meticulous technic are essential.<sup>32</sup> *Penicillin* promises to be the outstanding contribution to local burn treatment in every phase but the emergency dressing.<sup>30</sup> It had no effect upon the gram-negative bacilli, *B. proteus*, *B. pyocyaneus*, and *B. coli*, but a new agent, "*streptothricin*," shows promise in this direction. It is the by-product of one of the nonpathogenic soil actinomyces. Greater attention should be given to the possibility of *primary excision* of selected third degree burns and *immediate split thickness skin grafting*. The compressive type of dressing (discussed above) seems greatly superior to any leatherizing method of treatment; resilient compression greatly lessens further loss of plasma. At the same time the wound is well protected from further infection and the patient is allowed relative freedom of movement. The local care of the burn is reduced to a minimum for the first 10 to 14 days, during which time the dressing is left undisturbed.

The débridement of the badly devitalized tissues must be done with the greatest care lest living tissue be further injured, and with the healthiest respect for asepsis. The local therapy should be designed to discourage bacterial growth<sup>31</sup> and to prevent further contamination. The local therapy should also be designed to minimize plasma loss. When infection occurs, the local area must be treated as one would treat any other infected wound, by wide open drainage, thorough irrigation, and local and oral use of bacteriostatic agents.

**Use of Detergents:** Certain of the synthetic detergents, employed in one of several combinations, act as cleansing agents in the local treatment of burns.<sup>39</sup> Their unique properties which make them superior to other cleansing agents are (a) their ability to penetrate and "solubilize" substances such as greases, oils, and fats, as well as particulate matter; (b) their lack of either irritating or noticeable tissue-damaging properties as employed; (c) their antiseptic nature; and (d) the fact that, after grease, including the normal skin oils, is removed, the subsequent use of dye or tanning agent is rendered easier and a proper eschar more readily formed. The principle of employing a penetrant detergent, such as *sulfonated petroleum*, as a carrier for other more powerful detergents is especially valuable in so far as it greatly diminishes the amount of mechanical dispersion required to distribute the cleansing solution uniformly throughout an oil or grease layer.

**Chemotherapeutic Membranes —** Andrus, Nickel, and Schmelkes<sup>40</sup> report on 20 cases of second degree burns treated with hydrated films prepared from a hydrophilic cellulose derivative (methylcellulose). These transparent, thin, light, and tough films become pliable when placed in contact with the moist surface of a burn and follow its delicate contours. They adhere closely, remain transparent, permitting observation of the healing process, and are easily removed by simply sponging with water. If excessive oozing threatens to disintegrate the film, a second or third layer can be applied. By mounting these films on gauze, they can be given additional strength, and can be made into sheets large enough to encircle the torso of an adult. These films were medicated with *azochloramid* and *sulfanilamide*,

and became veritable performed chemotherapeutic eschars.

**Technic**—When the burn is first seen, it is débrided and cleaned with solution of sodium chloride or boric acid or azochloramid and sodium chloride as thoroughly as possible, sterile gloves and towels being used, but no anesthesia. All dead skin is removed at the first treatment. The preformed membrane is then applied directly to the raw oozing surface, the tissues being relied on to furnish sufficient moisture for the membrane to adhere. A dry sterile dressing is then placed over the membrane and held by plain gauze bandage. Daily smears and frequent cultures are taken. Good clinical results were achieved in all cases.

**Sulfadiazine**—In a comparative study between sulfadiazine spray and nonadherent pressure dressing, Meyer and Gradmann<sup>41</sup> found that this spray has all the disadvantages of other eschar forming agents. It is more difficult and painful to apply and more difficult to remove; reinfection frequently results, healing is incomplete, and second degree burns may be transformed into third degree. The combination of a chemotherapeutic agent applied as a nonadherent pressure dressing might be the procedure of choice. Regardless of the local treatment, the surgical principles of Koch must be applied if successful burn treatment is to be expected.

Maun, et al.,<sup>42</sup> found that most of the agents commonly employed in the treatment of burns have the ability to destroy normal tissues and thereby increase the depth of the burns. If they are used, one must be certain that the beneficial effects offset the harm done by the increased tissue damage. At present it would seem that eschar-forming agents produce the eschar over burned surfaces by necrotizing normal tissues. The alternative is to maintain a nonirritating substance over

the burn by a suitable dressing or adhesive attached to adjacent normal structures.

A monograph by the members of the staff of Massachusetts General Hospital on their experiences with 114 casualties of the Cocoanut Grove fire in Boston on November 28, 1942, gives many interesting phases of the management of these cases.<sup>43</sup> Particularly important are the findings pertaining to problems of hospital administration, social service activities, neuropsychiatric observations, resuscitation and sedation, roentgenology and pathology of pulmonary complications, rehabilitation, physical therapy, blood bank, thrombophlebitis, and metabolism. Of the 39 living patients, but one type of surface treatment was applied to burns of the skin. A bland ointment with protective dressing (sterile boric ointment strips) was applied without any preliminary débridement or cleansing, and antibacterial chemotherapy was given internally. The advantage of this treatment lies in its simplicity. The available personnel is freed for the care of shock and anoxia, yet the surface wounds need not be neglected. It is felt that this method should be of particular interest to the Armed Forces. For further details the reader is referred to this monograph.

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## CHEMOTHERAPY

### Gramicidin and Penicillin

**Gramicidin** — Gramicidin (*tyrothricin*) is a highly effective antibacterial substance for most gram-positive pathogens. It is considerably less toxic for tissue than most germicides in use at present.<sup>44</sup> Gramicidin behaves like an anionic detergent and is hemolytic. For this reason its clinical use is restricted to local application and to implanting it into infected cavities. A review of 142

cases in which crude gramicidin has been used indicates that approximately four-fifths of the results could be considered good or better. Therapeutic failures occurred in approximately a fifth of these cases. The results vary somewhat depending on the type of lesion and the organism identified.

**Penicillin**—Experimental and clinical studies indicate that penicillin is also a highly effective antibacterial agent against a variety of pathogenic organisms. Penicillin is even less toxic for tissues than gramicidin. Penicillin does not behave as a detergent-like substance and is not hemolytic. Penicillin may be administered locally, subcutaneously, intramuscularly, or intravenously without evidence of toxicity, and should prove of great value in the treatment of severe infections. In using penicillin the principles concerned with its somewhat selective antibacterial activity should be adhered to strictly. Neither gramicidin nor penicillin can be substituted for sound medical and surgical judgment so essential in the management of bacterial infections.

### Sulfonamides

The sulfonamide drugs are powerful chemotherapeutic agents. Their mode of action is not known accurately, but it is probable that bacteriostasis rests upon the inactivation of an enzyme or enzyme-substrate system necessary for bacterial growth.<sup>45</sup> Peptone, para-amino-benzoic acid, necrotic tissue, and certain bacterial and yeast extracts inhibit the bacteriostatic action of these drugs. The sulfonamides are essentially bacteriostatic, not bacteriocidal, and the natural defense mechanisms of the body have to complete the destruction of the bacteria. Sulfonamides inhibit bacterial growth, and prevent overwhelming intoxication by bacterial infection but tissue immunity must



be mobilized to realize complete recovery.

**Dosage** — Optimum concentrations should be obtained rapidly by a large initial dose, and this concentration should be maintained for 72 hours. If the drug is effective, beneficial results should be obtained by the third or fourth day at the latest. The drug should be discontinued if ineffective.

**Sulfathiazole** is regarded as the drug of choice for staphylococcal infections, but, clinically, it is probably no more effective than **sulfadiazine**, which is slightly less toxic. For all other infections which are susceptible to the sulfonamides, sulfadiazine is the drug of choice. For the normal adult, the initial dose is 4 to 6 Gm. (60 to 90 gr.), followed by 1 Gm. (15 gr.) orally every four hours day and night. If oral medication is interdicted, **sodium sulfathiazole** or **sodium sulfadiazine** may be given intravenously. The initial dose is 5 Gm. (75 gr.) given as a 5 per cent solution in sterile distilled water. The subsequent daily dose for sulfadiazine is 5 Gm. (75 gr.), one-half of it to be given in the morning and one-half in the evening. For sulfathiazole  $1\frac{1}{2}$  to 2 Gm. ( $22\frac{1}{2}$  to 30 gr.) should be given every 6 hours. By this method of administration approximately uniform blood concentrations will be maintained. The dosage of sulfonamide for local use is approximately 0.10 Gm. (1.5 gr.) per square inch. Up to 20 Gm. (300 gr.) may be instilled into larger wounds. Never use **sodium sulfapyridine** for local implantation, because it is so alkaline. For **succinylsulfathiazole** the initial dose is 0.25 Gm. (4 gr.) per Kg. of body weight and the subsequent daily doses is 0.25 Gm. (4 gr.) per Kg. given in 6 divided doses. Larger doses are tolerated if given at hourly intervals, and up to 0.5 Gm. (8 gr.) per Kg. per day may

be given with safety. The sulfonamides are merely adjuncts to surgery of the gastrointestinal tract and should never nullify the observance of well-established surgical principles in pre- and postoperative care.

**Carbamide-Sulfonamide** — According to Holder and McKay,<sup>46</sup> wound therapy with carbamide-sulfonamide mixtures is simple and inexpensive; results are excellent. Application as a first aid measure is most useful in prolonging the period during which it is safe to do definitive surgery. Carbamide through a process of chemical débridement has been shown to have many virtues in the treatment of contaminated and infected wounds. By its combination in topical application with the sulfonamide drugs the applicability of carbamide in wound therapy has been greatly extended. Carbamide removes the source of all and directly antagonizes at least some sulfonamide inhibitors as well as markedly increasing the solubility of the sulfonamide drugs. These factors all contribute to enhancing the efficacy of the sulfonamides. Ilfeld<sup>47</sup> agrees with these conclusions and outlines the treatment for compound fractures and traumatic wounds as follows:

**Treatment**—For emergencies, sprinkle **carbamide-sulfonamide mixture** in powder form over the wound, followed by dry dressing and an elastic or Ace bandage. Fractures are splinted. Following recovery from shock the patient is taken to the operating room. The part is scrubbed with soap and water for 20 minutes and the wound itself is cleansed with sterile sponges or cotton pledgets wet with sterile normal saline solution. The skin may be prepared further with ether and tincture of mercuric cresin or merthiolate. No antiseptic is used in the wound. After draping, irrigate the wound with 1000 cc. of normal



saline followed by 500 cc. of a **saturated solution of carbamide-sulfonamide** mixture in sterile water. Careful and thorough débridement (partial excision or saucerization of the wound) is then carried out under strict aseptic conditions. Irrigation is then repeated with first a normal saline and then a saturated carbamide-sulfonamide mixture solution. Reduction of the fracture is accomplished by traction; when indicated, a bone plate may be employed. The surgical procedure proper having been completed, about one to six ounces of **carbamide-sulfonamide mixture powder** are sprinkled and packed into every part of the wound. It is important that no area be overlooked. No attempt is made to close the various layers of the wound; the skin alone is approximated by means of a perpendicular mattress suture of silk. Immobilization is achieved either by internal fixation or by applying a plaster-of-Paris cast. Unless there is evidence of spreading infection, the wound is left alone and is not inspected until the seventh to the tenth day; skin sutures are removed after this time.

Contrary to most of the data given so far in this article, the findings of the Subcommittee on Surgical Infections of the National Research Council<sup>48</sup> indicate that the sulfonamides minimize the general spread of infections and cut down the incidence of septicemia and death. *There is no evidence that they lessen the incidence of local infection when applied locally.* To lessen the incidence of local infection in war wounds and burns, some other forms of the sulfonamides or some other bacteriostatic agents must be found which will be effective against the contaminating organism in the presence of damaged tissue.

In further elucidation of this point, Koch<sup>49</sup> points out that successful chemotherapy depends upon the specific effect

of a drug upon a specific infectious agent. The topical application of sulfonamide crystals is contrary to this concept in two respects: First, there is established locally a concentration of drug known to be toxic systemically; secondly, it is proposed to broaden the action of the drugs to include an effect upon relatively insensitive bacteria by increasing the concentration of the chemical agent. There has been no factual data provided for analysis of the extent to which such treatment has prevented the growth of bacteria in wounds.

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## THE EXTREMITIES

### Use of the Tourniquet

Duncan and Blalock<sup>50</sup> present experimental findings which confirm previous studies that a tourniquet should be used for the control of bleeding only if other means are not available or will not suffice. If the extremity is badly damaged and if a tourniquet has been in place for several hours when the patient reaches the point where definitive treatment may be employed, amputation is usually advisable. The harmful effects of a tourniquet will be lessened if the temperature of the part distal to the constriction is lowered by the application of ice; this is usually not possible under emergency conditions.

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## FRACTURES

### Gunshot Fractures

According to Kernwein,<sup>51</sup> the almost universally accepted treatment of compound fractures by surgeons in combat areas is as follows:

The patient is placed on an orthopedic table if one is available and fixed so that traction can be applied. The skin is cleansed with soap and water if facilities permit. If the patient is near the front

or with a mobile unit where water is scarce, washing is minimized. Antiseptics should not be placed in the wound, but they are often used to paint the intact skin about the wound. Excision of the skin wound is followed by reducing the fracture. Only spicules of bone completely detached from the periosteum and displaced at some distance from their bed should be removed. The wound is packed open but not tightly, as such a procedure has all the disadvantages and none of the advantages of primary closure. Steel pins of the Steinman type are cheap, of little bulk, and so easy to use that they should be included in even the meager equipment allowed mobile units. To put a steel pin through the calcaneus and incorporate it in a cast requires little or no additional time, yet greatly enhances the chances of maintaining good reduction. The cast is the ideal means of immobilization. It is cheap, rapid in application, easily transportable, and readily obtainable, in contrast to metals, and gives excellent immobilization. Patients in casts are more easily handled than patients who have been immobilized by any other means.

### **Compound Comminuted Fractures of Long Bones**

Searls and Harral<sup>52</sup> report the following observations on the late treatment of compound fractures sustained in enemy action. The interval between injury and definitive treatment remains all-important. In their series this interval varied between 25 minutes and three weeks. The administration of morphine in 0.03 Gm. ( $\frac{1}{2}$  gr.) doses on the field has added immeasurably to the comfort of the injured during many instances of tedious and back-breaking evacuation to the field hospital. The authors have been impressed with the better response of the wound to a mixture of sulfanilamide and

zinc peroxide under the vaseline pack than to sulfanilamide alone. The institution of postural (gravity) drainage immediately is advised in all cases of injury to the thigh. Early restitution of muscular tone should be the goal. The joints may be more quickly rehabilitated if muscular tone is maintained by various exercises while the joints are immobilized in plaster. The value of whirlpool baths, using soapy water, is pointed out as another means of speeding the healing of wounds. In addition, small doses of ultraviolet light are beneficial. Electrothermic excision and continuous salt bath arrests the progress of phagedenic ulceration. Skin grafting of all denuded areas is of great value. Response to the administration of penicillin is highly gratifying.

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## **THE HEAD**

The treatment of head injuries is not primarily a problem for the neurosurgeon, but rather for the general surgeon and the general practitioner.<sup>53</sup> If the patient has evidence of a head injury plus signs of shock, the head injury should be disregarded, except for the simple control of superficial hemorrhage, until the shock has been controlled or greatly improved. A quick but thorough examination of extremities, spine, chest, and abdomen should never be neglected.

### **Operative Head Injuries**

**Compound Fractures, Linear or Depressed**—After shaving and cleansing a large area around the open scalp wound, sterile fingers are used to separate the edges and to probe its depths for evidence of fracture. If no fracture is found, or if there is only a linear crack, the wound is thoroughly irrigated with sterile saline, the skin edges débrided, and closure effected by using interrupted

sutures of cotton or silk in the galea and skin. If considerable time has elapsed since injury, or if the wound is grossly contaminated, *sulfanilamide* may be placed in the wound before closure, but *sulfathiazole* should never be used, for it has been conclusively demonstrated that this substance may cause violent convulsions when in contact with the brain.

If the inspecting finger encounters comminution and depression of fragments, a radical débridement is necessary. Shave widely around the wound and then with soap, water, and alcohol prepare a circular area around the periphery of the field. This area is then infiltrated with 0.5 per cent *procaine* solution containing three drops of *adrenalin* to the ounce. Thorough irrigation and cleansing may then be done without pain to the patient. The field is then carefully draped, the operator's gloves changed, and the actual débridement begun. Bleeding from readily accessible torn vessels should be controlled either by the use of the electrocoagulation unit or silver clips. Then, with suction, macerated and hemorrhagic brain tissue is removed, and any bleeding vessels encountered are drawn up into the suction tip and occluded either by coagulation or silver clip. When the obviously destroyed cerebral tissue has been removed, it is wise to pack loosely the field with cotton or cottonoid moistened in normal saline at about 105° F. for a few moments. No normal brain tissue should be removed. When the field is dry the dura is sutured with interrupted sutures of fine cotton or silk, previously waxed with bone wax. After the dura has been closed, bone fragments may be replaced if the operator feels that the wound is free of infection, but if doubt exists they should be left out. The rest of the closure is done in layers, including the

periosteum if possible, with interrupted sutures. No drain is used. If the possibility of infection is definite in spite of thorough débridement, *sulfanilamide* may be used in the wound—merely enough to give a covering about 1 mm. in thickness. Postoperative care consists of careful nursing, adequate fluid intake, and bed rest with the head elevated to minimize bleeding. The patient should be allowed up in a wheelchair in eight to ten days and should be able to begin some sort of light duty in three to four weeks.

Siris<sup>54</sup> agrees with Furlow concerning the management of operative head injuries. He further states that in many instances fatalities from brain injury are not attributable to intracranial hypertension alone. There is evidence to indicate that edema, congestion, contusion, and laceration of the brain may seriously impair its ability to oxidize glucose. *Oxygen administration* is useful and *glucose administration* is of value, but its beneficial effects are due more to direct influence upon cerebral metabolism than to the dehydrative properties of the hypertonic solution. Carmody<sup>55</sup> presents a series of 12 cases of major gunshot wounds of the head; ten of them were complicated by severe infections. There were no deaths, as compared with a mortality rate approaching 60 per cent in World War I. Probably the difference is associated with more adequate fundamental therapy. Certainly the rôle of chemotherapy cannot be overemphasized, as *sulfanilamide* powder had been applied locally, supplemented by some form of parenteral administration. Also transporting the wounded by plane has proved its worth, particularly as this type of case stands transportation better preoperatively than within a few days postoperatively.

**Prophylaxis**—Money and Nelson,<sup>56</sup> while agreeing with the treatment as outlined above, have the following suggestions to make concerning the prevention of wounds of the head and subsequent infection:

1. The provision of a more modern design of steel helmet, which would fit closer and lower down over the frontal, temporal, mastoid, and occipital regions, and which would hinder the entry of rising foreign bodies from explosives which burst on the ground.

2. The issue of a general order that all troops should have the hair of the scalps closely clipped before going into battle. This would enable them to keep their scalps cleaner and greatly facilitate the work of the Medical Services in the recognition of wounds and their preparation for operation. It would also prevent long hairs and débris from being carried in by the missile.

3. Every soldier should be given, to keep with his field dressing, a large standard dose of *sulfapyridine* or *sulfadiazine*, 4 to 6 Gm. (60 to 90 gr.), with instructions to take it himself, if able, or have it given to him by a stretcher bearer, as soon as possible after being wounded. This would be an effective prophylactic for the next 12 hours.

### Nonoperative Head Injuries

**Spinal Puncture**—The great majority of head injuries do not require operation,<sup>53</sup> but the all-important thing is to be able to pick out those which do. Spinal puncture is never necessary as a routine procedure. It may, however, be valuable in diagnostic and therapeutic instances. A carefully done spinal puncture with measurement of pressure and examination of the fluid for blood may decide whether the individual may be promptly returned to duty or given proper care. As a therapeutic measure,

*spinal puncture* may be used to great advantage in the individual who, several days after an injury, develops a stiff neck, slight fever, and increased headache. The removal of 25 to 40 cc. of fluid containing hemolyzed red cells will give prompt relief and may be repeated if the occasion demands. Jugular pressure should not be applied, for this may, by increasing intracranial pressure, start fresh bleeding.

**Dehydration**—The important thing is to prevent the ingestion of large quantities of fluid; consequently, the patient with evidence of increased intracranial pressure but no signs of localized brain damage is given only 1000 to 1500 cc. of fluid daily, depending on age, sex, state of weather, etc.

**X-rays**—Radiographic examination is important and should always be made when the patient is in such a condition that the moving necessary to the procedure will not harm him. The equipment and technical skill must be such that decent pictures will result. There must be an individual present to read the films properly.

### Pathology

In practically every instance of fatal head injury there is a combination of pathologic processes.<sup>57</sup> For example, although the chief lesion may be an epidural hemorrhage, petechial hemorrhages and cerebral bruises frequently coexist. There is great variation in the extent and severity of brain lesions; in every case, gross lesions were found. A massive intracranial hemorrhage due to trauma is usually on the surface of the brain and may be amenable to surgical treatment. Large intracerebral clots are rare. In epidural hemorrhage, exploration about a fracture line seems justifiable. In subdural hemorrhage, a fracture line is of little value in localization,

often being opposite to the side of the subdural hemorrhage.

### THE HEART

While it is obvious that an operation is necessary in those instances of heart wounds in which bleeding continues, Blalock and Ravitch<sup>58</sup> believe that if a more conservative policy in regard to immediate operation is adopted in those instances in which there is not active bleeding through the chest wound or into the pleural cavity, the successful end results will be greater. Their recommendations for treating penetrating heart wounds with resulting tamponade are as follows:

(a) Aspirate the blood from the pericardium by the costoxiphoid route, if possible.

(b) Repeat if there is a recurrence.

(c) If it again recurs, perform a cardiorrhaphy through an extrapleural exposure.

If more than one aspiration is necessary, allow at least 15 minutes between paracenteses in order that the chances of closure of the wound by a clot may be increased. If there is good reason to believe an auricle rather than a ventricle has been injured, one may more safely defer operation. It should also be realized that there is a limit to the length of time (probably two hours) that tamponade may be allowed to persist.

### INFECTION

The treatment of infected wounds is ever changing and new substances are being added to the therapeutic armamentarium. The *chlorine-liberating mixtures* have been widely used over the past 20 years and by and large are credited with good results, when properly employed. *Zinc peroxide* has been shown to be specific for the anerobic

nonhemolytic streptococcus.<sup>59</sup> The popular drugs of today are the *sulfonamides* but a more critical evaluation of their worth (SEE: *Section on Chemotherapy*) is indicated lest they be forced to carry the burden of inadequate surgery and fall into disfavor. Nevertheless, they are in many respects the most ideal chemicals yet available for the treatment of the common infections. It must be remembered that success depends upon direct contact with the offending bacteria and that pus, necrotic tissue, and foreign material tend to prevent this contact. Furthermore, the lack of a demonstrable specific effect upon the anerobic bacteria requires that necrotic muscle and other substances conducive to a diminished available oxygen be removed. There remain, therefore, the principles of *débridement* and the *prevention of tissue ischemia* in treatment of all traumatic wounds. If these are always fulfilled much leeway remains in the later treatment, whereas if they are not adhered to the best methods are doomed to failure. *Penicillin* may, on the basis of its present limited clinical application, become the outstanding substance in the treatment of infection. It lacks toxic effects upon tissue and is lethal for a large number of bacteria in extremely low concentrations.

**Dettol** — *Dettol (Dett)* is a rapid acting germicide not grossly toxic to tissue but toxic to leukocytes. Beath,<sup>60</sup> in testing it on 100 cases of wounds of the hand, found that 86 healed by primary union in the most rigid sense; in eight cases infection was prevented; in only six cases did infection occur, but in them his form of treatment was not adequately given in essential features. This treatment is as follows: Infiltrate the tissues around the wound, putting the needle through sterilized clean skin at a distance from the wound edge; apply a tour-

niquet to the forearm to close the arteries completely; clip the fingernails short; wash the wound completely free of blood clot and macroscopic dirt, using a sterilized brush and dettol (5 per cent) solution, then soak the part for 45 minutes in dettol solution, and suture the wound. No débridement is done except where obviously nonviable tissue is present. The author emphasizes that antiseptics cannot supplant the removal of gross dirt from a wound or the judicious removal of nonviable tissue. They may supplement such procedures and the *sulfonamide drugs* may supplement both.

## THE NERVOUS SYSTEM

**Central Nervous System**—The recognition and treatment of shock, the use of the sulfonamides, the improved transportation of the wounded by air, land, and sea, and a more comprehensive conception of the physiologic effect of trauma have almost revolutionized the treatment of wounds of the central nervous system, according to Craig.<sup>61</sup>

In previous wars the mortality in wounds of the brain was greatly increased by shock and infection. Transfusions of blood, plasma, and albumin administered in sufficient quantities to combat shock have made possible the transportation of patients over long distances. The emergency treatment of open head wounds, consisting of shaving the scalp, arrest of hemorrhage, and local application and oral administration of *sulfonamides* have allowed for an interval before reparative surgery of from 36 to 48 hours. These two factors have not only lowered the mortality and reduced the incidence of infection but have changed the plan for the care of these cases; postoperative care and rehabilitation can be carried out simultaneously. Wounds of the spinal cord still produce

marked disability, depending upon the severity of the lesion, but the factor of infection has been moderated. Spinal shock caused by wounds of the contiguous structures has been noted and under proper treatment has shown a tendency to recovery in a large number of cases.

**The Peripheral Nerves**—War injuries to the peripheral nerves constitute one of the major problems confronting the medical officer.<sup>62</sup> So far the best results are obtained by *end-to-end anastomosis* without tension, without hemorrhage, and without infection. The *sulfonamides* do not inhibit nerve regeneration but allow for the suture of infected or potentially infected nerves, thus shortening the period which formerly was allowed for the infection to clear. Silk or cotton sutures are the accepted suture material but steel and tantalum wire are proving of value, being inert and not associated with any reaction on the part of the tissues. *Nerve grafts* and *fibrin glue* are not yet as efficacious as end-to-end suture. Subsequent slow extension of the joints with a secondary suture has been done with success. The blood supply of the nerves is important and should not be interfered with. Massage and passive motion is of value to keep the muscles in a condition which will be receptive to the regenerated nerve endings. Time for the nerve regeneration to take place should be allowed, but when in doubt it is much better to explore the nerves in which there is not a satisfactory functional recovery. At least from two to six months should be allowed for observation.

## PLASTIC SURGERY

### Division of Plastic Surgery

Maliniac<sup>63</sup> advocates a Division of Plastic Surgery in the Services, empowered to handle all injuries requiring

plastic repair, whether located on the face and jaws, neck, trunk, or extremities. Such a division must envisage three states of treatment: Early, intermediate, and late.

The front line surgeon should have some knowledge of the fundamentals of plastic repair, in order to prevent deformity and shorten the period of repair. The emergency measures may determine the course and final outcome of reconstruction.

The intermediate stage of treatment should be undertaken by well organized subdivisions of plastic surgery at base and general hospitals, with qualified specialists in attendance.

For the long, final stages of repair, patients requiring extensive plastic reconstruction must be segregated in special plastic centers, headed by a general plastic surgeon.

### Skin Grafting

**New Method**—Sano<sup>64</sup> presents 12 experimental cases in which she used a new method for skin grafting, depending upon the fixation of the graft by means of a thin coagulum of autogenous plasma. No stitches or pressure dressings are necessary. Autogenous heart blood is mixed in the proportion of 1 mg. of heparin to each 5 cc. of blood. This is then centrifuged, the plasma pipetted off, and kept in the refrigerator until needed. Tyrode's buffered salt solution is added to the packed red and white cells volumetrically, in the proportion of five parts to one part of red cells. This mixture is shaken vigorously and allowed to stand at room temperature for one-half hour. It is then centrifuged and the supernatant fluid (referred to subsequently as "extract") removed. The graft site is then painted with a drop or two of the heparinized plasma by means of a sterile fine camel's hair brush. Similarly, the

undersurface of the graft is painted with "extract." The graft is then placed on the denuded skin area and carefully fitted by means of forceps.

To produce fixation of the grafts through coagulation of the thin layer of plasma, hot compresses (at about 50° C.) are applied, using gentle pressure. The compresses are renewed frequently and maintained for between five and ten minutes. No dressings except one thickness of vaseline gauze to protect the tissue from infection are used. Stitches are not necessary. A cork ring is placed over the gauze to protect the operative field from trauma and this is held in place by adhesive tape. At the end of 24 hours the site of the graft is inspected, any serum which has accumulated around the edges gently wiped off, and the protective covering reapplied for from 48 hours to seven days, depending upon size and location. When properly carried out this procedure has resulted in 100 per cent takes. The method is being utilized successfully in clinical cases at Temple University Hospital.

**Tanning Agents Versus Vaseline Gauze**—Hirshfeld *et al.*<sup>65</sup> compared the reaction of normal tissues to tannic acid and to vaseline impregnated gauze by applying them to donor sites of individuals who were receiving skin grafts. It was found that donor sites treated by vaseline gauze healed more quickly than those treated by tannic acid. From study of biopsy specimens it was found that to form the eschar the tanning agents destroyed the dermis to a great depth. In addition, a marked leukocytic exudate was found beneath the eschar with further destruction of the collagenous bundles of the dermis. The portions of the epithelial structures contained in these layers were destroyed so that epithelialization finally took place beneath the exudate. Vaseline gauze proved to be nonirritating



to the exposed dermis; hence, only a mild red blood corpuscle and leukocytic exudate was found. The only visible damage to the dermis was in those cases showing some infection. Re-epithelialization from the uninjured dermal glands was more prompt in the donor sites treated by tanning agents.

### **Cutis Graft in Hernia Repair**

Cannaday<sup>66</sup> reports on ten cases in which cutis graft was used and concludes that it may be used in all cases in which the use of fascia or tendon might be indicated, with the expectation of superior results. It heals rapidly and well; is strong and stable from the time of operation; has great vitality; is able to survive under adverse conditions; possesses great tensile strength; has a good blood supply; gradually assumes the function of the part it replaces; is gradually converted into fibrous tissue, and is readily available when needed.

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## **SHOCK**

Wheeler defines shock as "a progressive vasoconstrictor oligemic anoxia."<sup>67</sup> Initiated by a loss of blood volume, it is continued by a series of physiologic disturbances, namely, lessened venous return to heart, decreased cardiac output, reflex vasoconstriction, hemoconcentration, fall in blood pressure, ischemia, and anoxia, and is perpetuated by hyperpotassemia, adrenal cortical insufficiency, or adrenal medullary overaction, histamine or tissue metabolites, and possibly nervous factors. The sequence of pathologic physiology produces a characteristic clinical picture.

### **Experimental Work**

**Protein and Fluid Balance**—In experimental shock produced by intestinal trauma, the plasma specific gravity and

protein concentration decrease as the shock progresses.<sup>68</sup> The albumin-globulin ratio of the fluid recovered at the site of trauma is greater than that of the circulating plasma. More albumin is lost in the early phase of shock; more globulin in the terminal phase. The major portion of fluid and protein lost from the circulation can be recovered at the site of trauma when the shock is not treated. This is not true when the shock is treated with plasma.

### **Amino Acids, Serum, and Plasma**

—In working with experimental animals, if the blood removed each time to produce shock was immediately replaced by the same volume of various solutions, significant differences were observed.<sup>69</sup> Survival time was unchanged with glucose in saline, increased to 4.2 hours with pure amino acids, to 5.15 with hydrolyzed protein. With citrated plasma or serum, survival time was but 4.5 and 4.6 hours, whereas with heparinized plasma it was 6.0 hours. From these and other findings, it may be inferred that in shock due to repeated hemorrhage a solution containing the amino acids and peptides of hydrolyzed protein has a beneficial influence as compared with glucose, and that heparinized is far superior to citrated plasma.

**Capillary Leakage**—According to Fine, Seligman, and Frank,<sup>70</sup> no evidence due to a change in the permeability of the general capillary bed was found. Tagged plasma proteins escaped into areas of injury in considerable amounts, but not into untraumatized areas. About one-fifth of the capillary blood becomes stagnant or trapped out of active circulation as the shock phase deepens. The progressive decline in shock is not due to a progressive fall in plasma volume but to a progressive fall in the volume of actively circulating plasma. This makes the therapeutic prob-

lem one of restoring volume and velocity flow through capillaries before the integrity of vital tissue processes is inevitably lost.

**Gelatin**—Parkins *et al.*<sup>71</sup> find that as a plasma substitute, gelatin is superior to saline. This is borne out by the higher total protein concentration following gelatin infusion, the considerably greater hemodilution, and the more rapid return of the blood pressure to normal. Resistance to repeated massive hemorrhage is markedly increased. Blood pressure was restored and maintained at approximately the same normal levels with gelatin as with plasma. The authors conclude that gelatin appears to be a suitable substitute for plasma, and that if a factor can be identified in plasma which accounts for its ability to maintain blood pressure in the severely burned animal during "acute toxemia," the addition of this factor to gelatin would probably result in a more adequate plasma substitute for burns.

### Treatment

**Diagnosis**—The early recognition of shock and its therapy depend on a knowledge of the physiologic changes occurring in the failing circulation. According to Mahoney and Howland,<sup>72</sup> there is no single diagnostic criterion by which impending circulatory failure may be recognized and at the present time the diagnosis depends on a general evaluation of the patient. The inadequacy of single hematocrit and plasma specific gravity determinations has been stressed. The plasma specific gravity may decrease rather than increase in the early stages of shock. Child<sup>73</sup> states further that because a diagnosis of impending shock is extremely difficult to make, every victim of a severe injury should be considered a potential candidate for the appearance of this complication.

**Prevention**—If every victim of an injury, no matter how superficially trivial, be considered potentially in shock and be kept under close observation for a period of a few hours before being subjected to any operative procedure, the appearance of shock can be effectively prevented. In recent years "shock wards" have been developed wherever an institution has found itself faced with the possibility of having to treat large numbers of injured persons. Even in traumatic surgery attempts to prevent the development of shock have been sufficiently successful to warrant their institution in every case.

**Types**—Although eventually a common therapeutic agent, effective in all types of shock, may be found, at the present time the various types of shock must be considered significantly different in their treatment. Hemorrhagic shock requires the early, rapid, and adequate *replacement of the blood* lost. Shock following burns demands *replacement of the plasma* lost. Empirical methods of treatment are useful, but *fluid replacement therapy* is essential. *Crystalloid solutions* should not be used in the treatment of shock, except in those patients presenting a severely deranged fluid and electrolyte balance.

Allen<sup>74</sup> draws the preliminary, but sweeping, conclusion that shock is reversible at all stages. However, if the treatment should be a specific and infallible cure of shock, there is no proof that a patient could stand the severest treatment that might be needed for the severest shock. Even if fatal, the large *saline infusions* at least gain time by preserving life through the most acute shock period, and there is the possibility that an antidote to the treatment may then be easier to find than a cure of the original shock. Restoration of the normal blood composition is an obvious under-

taking, either along with the saline infusion (perhaps with *dilute plasma*) or subsequently (perhaps with *concentrated plasma*). The fallacious theory of withdrawing water from the tissues by hypertonic saline injections proved acutely fatal in tests.

**Laboratory Aids**—The *red blood cell count* when taken alone as an index of the number of red cells in the body is not adequate, for factors in dehydration and overhydration may lead to false interpretations.<sup>75</sup> The *hemoglobin determination* parallels the red cell count in general and the same factors may give false clues as to actual conditions. A *white blood cell count* should be made in all cases, for it will serve as a base line in case of future complications; this is extremely important in burn cases. Differential counts should be made periodically. *Hematocrit or cell pack* is a particularly valuable test, as it is a mirror reflection of the cell volume of the circulating blood as contrasted with the total plasma or fluid fraction of the blood volume. If the volume of packed corpuscles is high in shock, it means that there is peripheral concentration regardless of cause. If the reading is low, it can mean only that there is cell loss and that replacement of red cells is necessary. The measurement of the *specific gravity of the plasma* is of great value, since it gives an accurate estimate of the state of hydration of the plasma fraction of the blood itself. *Total proteins* may likewise be fairly accurately calculated, and are singularly important in affecting the fluid balance of the body.

Brown<sup>75</sup> has found it expedient to maintain one or more qualified laboratory technicians on watch 24 hours a day to determine promptly the above mentioned tests. This is routine in all shock cases, and such measures are repeated as often as necessary. Any base hospi-

tal is equipped to carry out such measures. It must be remembered, however, that an accurate record of the vital signs together with *sound clinical judgment* are of paramount importance, and the laboratory is only an additional aid to the physician in the management of the patient's fluid needs.

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## THERAPEUTICS

*Edited by J. J. KOHLHAS, B.S., M.D.*

### PENICILLIN AND SULFONAMIDE THERAPY

HARRISON F. FLIPPIN, M.D., F.A.C.P., AND WILLIAM L. WHITE, M.S., M.D.

#### Penicillin

In 1929 Dr. Alexander Fleming, while working with staphylococcal variants, noted that among the usual air-borne contaminants there often appeared on his agar plates a certain mold which inhibited the growth of the surrounding staphylococcal colonies. His curiosity led him to identify this mold as a strain of *Penicillium notatum* and he found that by growing it in a simple nutrient broth he could obtain a readily filtrable active agent to which he gave the name "penic-

illin." He was able to demonstrate that many of the common pathogenic gram positive organisms and the pathogenic gram negative diplococci were inhibited by this substance; however, it had no effect upon the gram negative bacilli. This he applied to practical use by adding the filtrate to agar plates, which enabled him to grow the Pfeiffer bacillus of influenza without the troublesome overgrowth of gram positive cocci. He found that concentrates of the broth filtrate were nontoxic in animals and, when in-

jected into them, protected them against experimental infections. He, therefore, urged a study of the possible application of penicillin to treatment of disease in man.

Although Fleming and others continued to show interest in this antibiotic substance, particularly in its laboratory uses, it was not until 1940, 11 years after the original article, that a group at Oxford, including Chain, Florey, and others, began to work intensively upon methods of production, properties, and clinical uses of this material. In 1941, Abraham *et al.* published the results of their first clinical trials with penicillin. At about this time, stimulated by the British work, the Committee on Medical Research, in Washington, under the chairmanship of Dr. A. N. Richards, began to urge American manufacturers to undertake large scale production of penicillin—and many laboratories and clinics in the United States undertook to carry out laboratory and clinical studies on the new drug. Since that time production has steadily increased both in Britain and the United States so that further evaluation of the drug has been possible. In the United States the entire output of penicillin was frozen by the War Production Board and allocated to Army, Navy, United States Public Health Service, and to civilian research, through the Committee on Chemotherapeutics and Other Agents of the National Research Council.

**Production**—A high potency strain of *Penicillium notatum* is inoculated into the appropriate culture medium and after about seven to 14 days of growth the surface of the medium becomes covered with a wrinkled grayish-green pellicle, which exudes yellowish droplets containing the active substance, penicillin. By following the titer activity of the medium and the pH, the manufacturer deter-

mines the optimum time for halting incubation and harvesting the yield of penicillin. The most important cause of unsatisfactory yield is the occurrence of bacterial contamination of the culture, particularly with an organism such as *E. coli* which produces a penicillin-inhibitory substance known as penicillinase. The culture must be carefully guarded against such contamination.

At the peak concentration of penicillin in the liquid medium, it is separated from the mold by filtration or centrifugation and extracted with organic solvents. The final product is then obtained as a dry powder.

**Properties**—Penicillin is produced as either a sodium or calcium salt. The sodium salt has proved to be the most practical and is now used almost exclusively. Approximately 80 to 90 per cent of the crude final product is impurity.<sup>1</sup> The dry powder of the sodium salt is extremely hygroscopic and varies in color from yellow to brown; however, the pigment itself is not the active principle. Varying reports of its stability in the dry state have been made, but under anhydrous conditions at refrigeration temperature it does not lose any of its potency for three months if stored in sterile ampules. The material is quite soluble but when put into solution must be kept under aseptic conditions or refrigeration. It deteriorates slowly in aqueous solution at room temperature. The active principle is destroyed by boiling, by acids and alkalis, by certain heavy metals, by oxidizing agents and certain bacterial enzymes, especially penicillinase.<sup>2</sup> The preliminary empirical formula of  $C_{24}H_{32}O_{10}N_2Ba$  (for the barium salt) was suggested by Abraham *et al.*<sup>1</sup>

In its mode of action penicillin is bacteriostatic and not bactericidal in concentrations likely to be used therapeutically.<sup>2</sup> Therefore, in established infec-

tions, penicillin simply retards or stops bacterial multiplication, and the final elimination of the organisms is effected by the body defenses of the host. One of the main advantages of penicillin over the sulfonamides is the fact that its activity is not inhibited by the presence of large numbers of bacteria, by pus or tissue autolysates. There is no detectable destruction or absorption of the active element by inhibited organisms,<sup>3</sup> suggesting that its mode of action is indirect rather than direct.

**Absorption, Excretion, and Distribution**—Rammelkamp and Keefer,<sup>4</sup> after studying the absorption, excretion, and distribution of penicillin and reviewing the literature, summarize their findings as follows: "Intravenous injection of penicillin resulted in high initial concentration in the blood plasma which was followed by an abrupt fall. Traces of penicillin were found in the blood for 30 to 210 minutes after the injection, the length of time depending on the amount administered. The sharp fall noted in the serum concentration immediately after injection was associated with an increased excretion in the urine. The average excretion after intravenous injection was 58 per cent of the administered dose.

"Penicillin was rapidly absorbed when given intramuscularly and slowly absorbed after subcutaneous injections. Excretion in the urine was rapid following intramuscular injections and delayed after subcutaneous injections.

"Absorption from the body cavities was delayed, and this was reflected in the slow excretion of penicillin by the kidneys. The total amount found in the urine was somewhat lower than obtained following intravenous injection. Fluid aspirated from the pleural and joint cavities, 22 and 13 hours after the injection, showed appreciable amounts of penicillin remaining.

"Administration of penicillin by enteral routes showed that absorption from the duodenum was rapid, whereas oral and rectal doses were poorly absorbed. These findings may be explained by inactivating effect on penicillin of acid and *Escherichia coli*. After oral, intraduodenal, and rectal administration, the average amount excreted in the urine was extremely small.

"In the presence of renal failure, penicillin was not excreted rapidly, and as a result, high concentrations were maintained in the blood stream after intravenous injections.

"Studies on the distribution of penicillin showed that the substance failed to penetrate the red cells in significant amounts. In general, the average concentration found in erythrocytes was less than 10 per cent of the plasma concentration. No penicillin was found in the spinal fluid, saliva, or tears, in subjects receiving it intravenously."

Penicillin is destroyed by the hydrochloric acid in gastric juice, but is unaffected by saliva, bile, and succus entericus.<sup>5, 6</sup> It is excreted in the bile in greater concentrations than is found in the blood stream,<sup>7</sup> indicating that it may be excreted by the liver. If diodrast is administered with penicillin the rate of excretion is appreciably lowered.<sup>8</sup>

In normal subjects, following intrathecal injections, the rate of absorption from the spinal fluid and urinary excretion is slower than in patients with meningitis. The drug is detectable in the cerebrospinal fluid by both spinal drainage and cisternal tap for 24 hours after intrathecal administration. A pleocytosis has been observed in the cerebrospinal fluid of some cases following intrathecal administration of penicillin.<sup>9</sup>

All methods of determining the amount of penicillin in body fluids have been based on bioassay, titrating the unknown

against dilutions of known strength. The principal methods now in use may be classified as serial dilution methods, plate-cup methods, and turbidimetric evaluations. These tests vary a good deal in respect to accuracy, speed, and amount of labor involved. The plate-cup method seems most practical for routine purposes, particularly in gaining a rough impression as to the susceptibility of a given strain of bacteria.<sup>10</sup> A rapid and delicate test has been suggested by Rake and Jones,<sup>11</sup> making use of the hemolytic qualities of beta hemolytic streptococci. A small amount of red blood cells and a standard inoculation of streptococci are added to each tube of serial dilutions of both the fluid to be tested and the standard solution. The end-point is the appearance of hemolysis, which indicates lack of inhibition of growth.

All measurements of penicillin are in terms of units rather than milligrams, since the crude substance contains varying amounts of impurities. According to Florey and Jennings,<sup>12</sup> the unit is that amount of penicillin which, when dissolved in 50 cc. of meat-extract broth, just inhibits completely the growth of the test strain of *Staphylococcus aureus*.

**Route of Administration** — Since penicillin is destroyed by gastric juice<sup>13</sup> and by bacterial enzymes present in the rectum and intestines, it is necessary to resort to parenteral routes of administration; however, duodenal tube instillations have been moderately successful.<sup>2, 14</sup> As stated above, following subcutaneous injection of penicillin, the absorption is slow and the blood concentration is often inadequate; therefore, intravenous, intramuscular, and topical injection into the body spaces, both natural and pathological, have been found to be most practical. Since the drug is excreted so rapidly, a continuous intravenous infusion appears to be the most

logical, from the standpoint of maintaining high blood concentrations and economizing in the use of penicillin. This method of therapy presents many technical difficulties and, if supply presents no problem, the continuous intravenous infusion is best reserved for acute or moribund patients in much the same manner as the intravenous sodium salts of the sulfonamides are now used. Herrell<sup>6</sup> has demonstrated that low dosage, when administered by continuous drip, is quite effective. Because of the rapid excretion, if intramuscular injection is to be used, it is necessary that it be given frequently. Although the Floreys<sup>2</sup> have reported good results in one case of chronic osteomyelitis with intramuscular injections every sixth hour, it appears to be the consensus that administration every second or third hour is more effective. The site of intramuscular injection should be rotated between the larger muscle masses so as to insure adequate absorption and prevent concentrated local trauma. Topically, the dry sodium salt is very irritating to the tissues, but a solution containing 250 units per cc. has given good results in open infected wounds where the drug can be brought into adequate contact with the wound surface.<sup>1, 2, 15-17</sup> Clark, Colebrook, Gibson, and Thompson<sup>15</sup> reported excellent results in the treatment of infected burns in this manner. Local penicillin has also been used successfully in the treatment of eye and mastoid infections. It has been suggested that penicillin be injected into empyema cavities, pericardial spaces, joints and subarachnoid spaces where there is localized infection. Usually, systemic treatment alone does not produce therapeutically effective levels in these cavities.<sup>17</sup>

**Toxicity**—One of the most striking features of penicillin is the very low toxicity of the relatively crude product. It



has been shown that the drug has no harmful effects on mice when administered in therapeutically effective doses.<sup>18</sup> During its developmental period, various reactions were noted, but the constant improvement in the commercial products and the simultaneous decrease in toxic manifestations, leads to the conviction that many of the untoward reactions have been due to the impurities present rather than to the active substance itself.

**Chills and Fever**—Lyons<sup>1</sup> has shown that pyrogenicity of penicillin solutions could often be eliminated by Seitz filtration before injection. Many patients will experience a transient burning sensation at the site of intramuscular injection, but this is not a constant feature with any particular brand of penicillin nor is it constant in individual patients. Chills and fever occurred frequently with the impure products but are now seldom seen. They present no definite contraindication against continuance of therapy. There is no evidence that penicillin is antipyretic. A reduction in fever after treatment commences is usually indicative of a therapeutic response. On the other hand, it is at times difficult to determine whether or not a continuation of the febrile course is due to the infection or to a reaction to the drug.

Thrombophlebitis is often associated with continuous intravenous infusion of penicillin.<sup>1, 17</sup> It may be accompanied by chills and fever. Since pulmonary infarction as a consequence of thrombophlebitis in the lower extremities is a constant danger, it has been recommended that intravenous infusions of penicillin be given in the arm veins.<sup>1</sup> Robinson<sup>18</sup> has shown that 64 times the amount of the therapeutically effective dose is required to produce toxic effects in mice. Many of the animals which died following massive doses showed evidence of necrosis at the site of injection, indi-

cating that concentrated solutions of sodium salts are irritating to the tissues. Penicillin has a low cytotoxic effect upon tissue cultures.<sup>19</sup>

**Urticaria**—The most specific of the reactions to penicillin available today has been the development of generalized urticarial lesions which may occur at any time during the treatment, but are most commonly seen after the first week. This has appeared in less than 6 per cent of the patients treated.<sup>1, 17</sup> It may be transient and disappear quickly or it may persist for three to five days. The usual supportive measures with *epinephrine* or *ephedrine* have proved helpful. It is rarely necessary to discontinue therapy because of the development of an urticaria, and the rash frequently disappears while treatment is being continued. Tests for cutaneous and ophthalmic sensitivity after the rash disappeared have been negative. Precipitins against penicillin are absent even during the phase of urticaria. Heterophil agglutinins have been irregularly demonstrated by means of tests adjusted for maximum sensitivity but these have not been deemed significant. Transient azotemia has occurred during the course of penicillin treatment but promptly disappeared when the drug was stopped.<sup>1, 2</sup> This is a rare complication and may or may not be due to penicillin.

**Range of Therapeutic Effect**—In Fleming's original paper he noted inhibition of staphylococci, streptococci, gonococci, meningococci, *Corynebacterium diphtheriae*, and *B. anthracis*, but not of *E. coli*, *Haemophilus influenzae*, *Salmonella typhi*, *P. pyocyaneus*, *Bacillus proteus*, or *Vibrio cholerae*. The list of inhibited organisms has been extended to include most of the gram positive organisms. Repeated tests show lack of active effect on most of the gram negative bacilli, though susceptible variants have been described.<sup>20</sup> It appears that

certain definite penicillin-inhibitors are present as products of the growth of gram negative bacilli, especially the penicillinase produced by *E. coli*. Certain strains of gram positive organisms have been found to be resistant to penicillin. Among these are strains of *Staphylococcus albus*, *Streptococcus faecalis*, and *Clostridium tetanomorphum*.<sup>1, 20</sup>

**Penicillin Fastness**—Some strains of generally susceptible species have been shown to be resistant to penicillin without previous contact with the drug; however, this is not common.<sup>1</sup> Resistance to penicillin can be induced by growing it in progressively increasing concentrations of the drug.<sup>4, 21</sup> While there is usually no basic alteration in the cultural or bacteriological characteristics, there frequently results a loss of virulence. Since acquisition of fastness is always a possibility in prolonged therapy, it is wise to test the sensitivity of the organisms in each case. This can be most easily done with the plate-cup method. The theoretical danger of fastness makes it advisable to avoid prolonged treatment with inadequate doses of the drug.

**Dosage**—Dose schedules are adjusted according to the age and size of the individual, the acuteness, chronicity, and severity of the infection, the route of administration, and to the degree of susceptibility of the infecting organism in the individual case. Staphylococcal infections have responded to dosages varying from 30,000 units<sup>6</sup> per day to 360,000 units<sup>1</sup> per day, but usually require dosages of 100,000 to 200,000 units daily; while streptococcal and pneumococcal infections respond to more moderate doses. Meningococcal and gonococcal infections can often be treated satisfactorily with doses of 30,000 to 60,000 units each day. Streptococcal and pneumococcal infections require approximately 100,000 units.

In the treatment of pneumococcal pneumonia, three to seven days should be sufficient.<sup>17</sup> In the treatment of suppurative empyema and other streptococcal, pneumococcal, and staphylococcal infections of closed cavities, local instillation of 10,000 to 40,000 units of penicillin once or twice daily is usually adequate. In meningeal infections intrathecal injections should be given once or twice daily according to the severity of the infection, using 5000 to 10,000 units of penicillin in 5 to 10 cc. of physiological saline solution, respectively. A pleocytosis may occur in many patients with dosages of this strength but can often be avoided by reducing the concentration of the solution.<sup>9</sup>

**Clinical Results — Staphylococcal Infection**—Probably the most striking and consistent results with penicillin have been in the treatment of staphylococcal infections. Many cases have been reported of successful treatment of staphylococcal bacteremia, acute and chronic osteomyelitis, cavernous sinus thrombosis, staphylococcal lung abscesses, etc. This experience has gone far to establish the value of penicillin as a chemotherapeutic agent. Although occasional resistant strains have been encountered, the general susceptibility of the staphylococcus is usually great enough to permit effective therapy.

Since the staphylococcus is present in pure or mixed culture in a large proportion of chronic surgical infections, penicillin should be most useful in the treatment of these lesions. The acute infections produced by staphylococci, such as early acute hematogenous osteomyelitis, bacteremias originating from soft tissue foci, lung abscesses, etc., may respond to penicillin therapy without the necessity for surgical intervention. While the reported experience with penicillin as an adjunct to surgical treatment is still

quite limited, it has been possible to remove sequestra and chronically infected soft tissue, and to drain collections of pus with greater impunity and with less likelihood of septic reactions than has been heretofore possible.<sup>1</sup> In the presence of a localized collection of pus it is probably desirable to remove the bulk of the pus by aspiration or drainage.

A major problem in the treatment of chronic staphylococcal osteomyelitis has been the tendency of these cases to show late recurrence of infection in areas of bone and soft tissue which have previously been the sites of active lesions. The known susceptibility of the staphylococcus to penicillin offers the encouragement that a means may now be available to completely débride these seriously infected lesions without fear of systemic reaction or future reinfection.<sup>1</sup>

**Streptococcal Infections**—Among the streptococci some species have been found to be resistant to penicillin, such as the thermophilic nonhemolytic streptococci (*faecalis* type). Usually the beta hemolytic, the mesophilic nonhemolytic, and some of the alpha hemolytic streptococci are susceptible.<sup>1</sup> The use of penicillin in acute streptococcal infection has not yielded results which are significantly better than the usual results with the sulfonamides but it has been found to be of immeasurable value in the treatment of those infections which have become sulfonamide-fast or resistant.

Although the alpha hemolytic streptococcus is usually inhibited by penicillin, the results in the treatment of subacute bacterial endocarditis have been encouraging but by no means dramatic. While on a course of penicillin therapy, these patients may improve clinically and the blood culture become sterile, but, upon discontinuing the drug, relapses are common and often prompt.<sup>17</sup> In the case of

acute endocarditis due to pneumococci and staphylococci, penicillin has been of relatively little value though occasionally there may be a temporary arrest of the lesion while the patient is under treatment.

**Pneumococcal Infection**—Since sulfonamide therapy has appeared to be adequate in the treatment of most cases of pneumococcal pneumonia, not associated with complications and, since the superiority of penicillin has not yet been established, it may not be necessary to subject all patients with this disease to the discomfort of a course of penicillin therapy; however, the use of this drug in the treatment of sulfonamide-resistant pneumonia has been shown to be highly successful. In the treatment of pneumococcal empyema, penicillin appears to be superior to the sulfonamides.<sup>17</sup> Results to date with penicillin in pneumococcal meningitis have not been significantly better than those with the sulfonamides.

**Gonococcal and Meningococcal Infections**—Just as in the case of pneumococcal pneumonia, penicillin is an adequate agent in the treatment of gonococcal and meningococcal infections, but its use in all cases is perhaps unwarranted because of the laborious method of its administration. There is clear indication for its use in those cases where the sulfonamides are for some reason contraindicated or where there is evidence of sulfonamide fastness. The results in the treatment of sulfonamide-resistant gonorrhea have been spectacular.<sup>17, 21, 22</sup> (SEE: Venereal Diseases.)

**Clostridial Infection**—Both *in vitro* and *in vivo* laboratory studies have shown that the pathogenic clostridia are inhibited by penicillin,<sup>5, 20</sup> but thus far the clinical experience has been meager. It should be pointed out that penicillin inhibits these organisms but there is no

evidence that it alters the toxins produced by them and hence should be used in conjunction with ample dosage of specific antitoxin.

***Spirochetal Infection*** — Mahoney<sup>23</sup> has reported good results with penicillin in the treatment of acute syphilis, while O'Leary and Herrell<sup>24</sup> have reported a case of secondary syphilis which responded to therapy. It is conceivable that Vincent's infection, yaws, Weil's disease, relapsing fever, etc., may likewise respond to penicillin treatment.

***Other Infections*** — It may be expected that penicillin will be effective in the treatment of anthrax and diphtheria. It will probably be of little use in the treatment of gram negative bacillary infections, virus diseases, mycotic infections, and plasmodial infestations. Thus far it has not been shown to be of value in tuberculosis but there are encouraging reports on its use in actinomycosis.

### Sulfamerazine

**Introduction**—It is generally recognized that sulfadiazine, by virtue of its equal or superior antibacterial efficacy and its relatively low toxicity, is the most satisfactory of the sulfonamide compounds now in common use.<sup>27</sup> Despite these attributes, sulfadiazine is not an ideal chemotherapeutic agent, since certain shortcomings are apparent: (1) The drug is slowly absorbed from the gastrointestinal tract, and (2) at times gives rise to serious toxic reactions, particularly in the urinary tract.<sup>28</sup> Attempts to find a drug possessing definite superiority for clinical use over sulfadiazine have directed attention to the methyl derivatives of sulfadiazine. Of these, sulfamerazine has warranted clinical trial because of its therapeutic effectiveness against experimental infections, its pharmacologic behavior, and its relatively low toxicity in animals.

Sulfamerazine (2 - sulfanilamido - 4 - methyl - pyrimidine, sulfamethyldiazine), synthesized by two groups of investigators, is one of the methyl homologues of sulfadiazine. The therapeutic activity of sulfamerazine was described by Roblin, Williams, Winnek, and English at the same time that they reported on that of sulfadiazine. It was found that both of these drugs were considerably more active against streptococcal, pneumococcal, and staphylococcal infections in mice than sulfanilamide, sulfapyridine, or sulfathiazole. Pharmacologic studies by Welch, Mattis, Latven, Benson, and Shiels<sup>29</sup> in various species of laboratory animals have indicated that sulfamerazine is more rapidly and more completely absorbed from the gastrointestinal tract and more slowly excreted by the kidney than is sulfadiazine. Toxicologic observations by this same group of workers suggested that sulfamerazine is no more toxic in experimental animals than is sulfadiazine, when a comparison is made on the basis of blood concentration of the drugs. In these toxicity experiments, particular attention was given to the possibility of neuropathologic changes, because of past clinical experience with the sulfonamides containing a methyl group (sulfamethylthiazole, sulfanilyl dimethyl-sulfanilamide).<sup>30</sup> It was found that dogs or monkeys, given large doses of sulfamerazine over 30-day periods, showed no evidence of nerve injury, but chickens with high blood concentration of the drug developed definite nerve lesions, although the changes were no greater than those resulting from lower blood levels of sulfadiazine in the same species.

**Clinical Observations — Absorption, Distribution, and Excretion Studies**—Oral administration of a single dose of 3 Gm. (45 grains) of sulfamera-

zine is followed by a rapid rise in its concentration in plasma to higher levels that are sustained for a longer period of time than after ingestion of the same amount of sulfadiazine.<sup>29, 31, 32</sup> Patients receiving 1 Gm. (15 grains) every four hours after the initial 3 Gm. (45 grains) dose maintained an average plasma concentration of free sulfamerazine of 15.4 mg. per 100 cc.; those who received 1 Gm. (15 grains) every six hours, 12.7 mg. per 100 cc., and those who received 1 Gm. (15 grains) every eight hours, 10.9 mg. per 100 cc. Acetylation occurred to the same extent as with sulfadiazine, an average of about 15 per cent of the total concentration of sulfamerazine in plasma being present in acetylated form.<sup>33</sup> Sulfamerazine resembles sulfathiazole in that the erythrocytes contain much lower concentrations than the plasma.<sup>31, 32</sup> For this reason determinations on serum or plasma are more informative than those made on whole blood. In cerebrospinal, pleural, and ascitic fluids concentrations of sulfamerazine appear to be comparable to those of sulfadiazine.

The higher concentrations of sulfamerazine in blood, compared with other sulfonamides, is in part due to more complete absorption from the gastrointestinal tract and in part due to the slower rate of excretion.<sup>29</sup> Sulfamerazine and its acetyl derivative are more soluble in urine than are the corresponding forms of sulfadiazine. Increasing the urine pH from 6 to 7 nearly doubles the solubility of both free and acetylsulfamerazine. Because of the great solubility and smaller amounts required to produce a given blood level and therapeutic response, the likelihood of crystal and concretum formation in the urinary tract is distinctly less than with sulfadiazine. However, the smaller intake of drug is offset to some

extent by the more complete absorption of sulfamerazine.

**Sulfamerazine Dosage**—In general, the drug is given orally, with an initial dose of 3 Gm. (45 grains), followed by 1 Gm. (15 grains) every four, six, or eight hours, depending on the nature of the infection, until the temperature remains normal for 48 to 72 hours. In severe infections, such as meningitis, encephalitis, or peritonitis, the initial 3 Gm. (45 grains) is best administered by vein (5 per cent solution of sulfamerazine sodium in distilled water) and followed by 1 Gm. (15 grains) by mouth every four hours.

**Therapeutic Results** — Insufficient clinical data do not permit at this date a comparison of the therapeutic effectiveness of sulfamerazine with the other sulfonamides now in general use. However, personal clinical experience with sulfamerazine,<sup>33, 34, 35</sup> combined with the reports of others,<sup>36, 37, 38</sup> suggests that this drug is equally as effective as any of the other compounds in the treatment of infections due to the pneumococcus, meningococcus, streptococcus, and possibly the staphylococcus. Preliminary observations also indicate the effectiveness of sulfamerazine in the control of the more common types of urinary tract infection.

**Toxic Manifestations**—In a group of 400 patients treated with sulfamerazine, 48 toxic reactions attributable to the drug were noted in 38 of the patients (9.5 per cent).<sup>33</sup>

**Urinary Tract Complications**—As mentioned above, one of the most significant difficulties associated with the use of *sulfadiazine* is its toxic effect upon the urinary tract, namely, hematuria, urinary suppression, and renal colic. These complications are due in part, if not entirely, to the relative insolubility of sulfadiazine, especially its

acetyl fraction. In view of the greater solubility of both sulfamerazine and acetylsulfamerazine in urine, as compared with sulfadiazine and acetylsulfadiazine, one might expect to encounter less urinary tract toxicity with the former. Crystalluria, presumably due to the drug, was observed in approximately 15 per cent of the cases, but this finding was not considered as being significant unless it was associated with other urinary complications. Likewise, the presence of occasional red blood cells in urine was not classified as an urinary abnormality due to sulfamerazine because of the frequency with which microscopic hematuria is present with acute infections. Gross hematuria occurred in five patients (1.3 per cent), four of which experienced acute loin pain. In four of this subgroup (aged 20, 15, 55, and 18 years) acute loin pain and gross hematuria developed on the first, fifth, tenth, and fourteenth days of treatment following 4, 16, 36, and 77 Gm. of the drug, respectively. The urine in these cases contained many drug crystals as well as innumerable red blood cells. For each patient in this group the urinary output was 1200 cc., or better, for the 24-hour periods preceding, the day of, and following the apparent ureteral blockage. In each instance the drug was stopped immediately and within 24 hours after the attack none of the patients offered any symptoms or laboratory evidence of any urinary tract disturbances. All of the above cases recovered. The fifth case, a 30-year-old male, suffering with subacute bacterial endocarditis, received 14 Gm. of the drug during the first three days of treatment with no apparent untoward effect. On the fourth day he was given 25 Gm. (sulfamerazine sodium) intravenously over a 30-minute period. A free drug level, taken one hour after the infusion, was 106 mg. per 100 cc. of serum. The first voided specimen

of urine thereafter contained many drug crystals and innumerable red blood cells. With the exception of the finding of occasional red blood cells in the urine throughout the next 48 hours and the partial suppression of urinary output for several days, there was no other evidence of renal damage. After five days, the patient was again given sulfamerazine by mouth with no further urinary disturbances. The patient finally died and sections of the kidneys were examined and no renal damage was found which could be attributed to the drug. It is possible that some of these urinary tract complications might have been prevented or minimized had alkalis been employed. At least, the fact that urinary complications occurred makes the routine use of alkalis advisable.

**Dermatitis**—Skin rashes, developing during sulfamerazine treatment, were encountered in 12 patients (3 per cent). The rash was scarlatiniform in four and maculopapular or morbilliform in the others. These eruptions were observed in only two cases before the seventh day of therapy; in these it appeared on the fourth and fifth days, respectively.

**Nausea and Vomiting**—In this series there were five patients (1.3 per cent) in whom nausea and vomiting occurred, which we attributed to sulfamerazine. There were cases with vomiting before the drug was given which have been excluded, but in these the vomiting usually ceased after the infection was brought under control. In none of the patients with nausea and vomiting following the administration of sulfamerazine was it necessary to stop chemotherapy because of this toxic effect.

**Blood Disturbances**—Nine patients (2.3 per cent) developed leukopenia (less than 4000 leukocytes per cmm.) between the sixth and twelfth day of treatment with sulfamerazine. In two the total



white count returned to normal, although the drug was continued, whereas in six the total white count became normal soon after the withdrawal of sulfamerazine. The ninth patient was the case of subacute bacterial endocarditis mentioned previously, who received massive dosage of the drug and developed a thrombocytopenia as well as a leukopenia. A biopsy revealed a generalized hypoplasia of the bone marrow, although within two weeks after the drug was stopped the peripheral blood picture returned to normal.

**Drug Fever**—A diagnosis of drug fever was made in eight patients (2 per cent) receiving sulfamerazine. The fever in these cases was encountered between the fifth and fourteenth days of treatment.

**Mental Manifestations**—Although it is often difficult to determine whether certain neuropathologic changes are due to the drug or the disease, we have made the diagnosis of drug psychosis in four patients (1 per cent). In two of these, the mental symptoms subsided promptly after the drug was stopped, whereas in the others the mental changes gradually cleared, although the drug was continued.

**Summary and Conclusions**—From a pharmacologic standpoint, it appears that sulfamerazine is a more satisfactory drug than sulfadiazine in that higher blood levels are attained more rapidly and sustained longer by sulfamerazine than by similar amounts of sulfadiazine. Thus, it is possible to maintain a given concentration of drug in the blood with smaller amounts of sulfamerazine than sulfadiazine. Likewise, this feature of sulfamerazine may prove it to be superior to sulfadiazine as a prophylactic agent. Furthermore, the rapid absorption obtained with sulfamerazine frequently makes the parenteral use of the drug unnecessary.

The therapeutic results obtained with sulfamerazine in the cases of pneumococ-

cal and meningococcal infections are comparable in every respect with the results obtained with sulfadiazine.<sup>33, 39</sup> In the other conditions in which sulfamerazine was employed the limited number of cases involved prevents a definite comparison, although it appears that sulfamerazine is as effective as sulfadiazine in the various infections in which it was used. In general, the toxicity of sulfamerazine is low<sup>33, 36, 37, 38, 40</sup> and is no greater than that of sulfadiazine.

It appears that sulfamerazine, by virtue of its pharmacologic behavior, therapeutic efficacy, and low toxicity offers definite advantages over sulfadiazine and is worthy of extensive clinical trial.

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## ADDITIONAL THERAPEUTIC CONSIDERATIONS

J. J. KOHLHAS, B.S., M.D.

### Additions to Blood Replacement Therapy

In anemia, where the increase of red cells is indicated, Alt<sup>1</sup> has demonstrated the effectiveness of red blood cell transfusions. English workers have also used this method and point out that it is especially effective in anemias where cardiac insufficiency plays an important part. The widespread preparation of plasma makes available tremendous quantities of red cells at a much lower cost than that of securing whole blood in conditions where erythrocytes alone will suffice. Alt<sup>1</sup> points out the effectiveness of this type of transfusion in the anemia of leukemia. Younger cells (less than three days old) are used in this condition because of the shortness of life of transfused cells. No cells are recommended to be transfused which have been stored more than seven days in any anemias. Cells can be transfused in their concentrated form with the addition of little or

no solution, but there seems to be no reason why the cells from a liter of blood should not be diluted in from 100 to 500 cc. of saline solution.

Reactions to this type of transfusion were reported by Robert Evans,<sup>2</sup> with an incidence of seven reactions in 44 procedures. All the reactions were of a febrile nature. They found no evidence that free hemoglobin in the plasma was a factor in production of febrile reactions. Hemolytic reactions due to anti-Rh agglutinin have been reported. It must be remembered that, unlike serum transfusions, red cells must be typed and cross-agglutinated before administration. This procedure bids fair to become more widely used in the treatment of anemias.

Red cell reinfusion while taking blood from donors when this blood is being used to secure plasma is a valuable procedure. Co Tui *et al.*<sup>3</sup> studied the effect of reinfusing red blood cells in plasma donors. It is interesting to note that the

bilirubin level and reticulocyte count remained normal despite full weekly blood donations in three patients carefully observed over a period of nine weeks or more. They recommended that reinfusion be undertaken where malnutrition of the donating population is evident or where a large portion of the donors are women.

Another instance of the value of reinfusion of red blood cells might seem to be bleeding to relieve uremia. Bleeding can be practiced as a method of relieving the system of some of the uremic products. This carries with it the possibility of causing a severe anemia. By means of the reinfusion of red cells the anemia so produced can be averted and the method becomes more practical. Furthermore, a certain percentage of valuable protein is returned to the blood which may favorably elevate the oncotic pressure.

### Synthetic Analgesic

Demerol is one of the compounds of the piperidine series. Its chemical structure resembles atropine, and it has certain of the pharmacological properties of the latter. It was unexpectedly found that this drug possessed analgesic effects comparable to morphine. In fact, its pharmacologic actions can be classified into analgesia, spasmolysis, and sedation. It is reported as not depressing the central nervous system to the same extent as morphine. Studies have been carried out to determine effective dosage and the possibility of addiction. Demerol was synthesized in Germany in 1939 and brought to this country shortly before the war. Hoffman<sup>4</sup> found it effective and safe in cases of nonoperable carcinoma, for preparation for cystoscopy, and ureteral catheterization and irrigation, in arthritis, thoracentesis, and for the root pains of tabes. He also reported its use

in five patients with coronary sclerosis, two of whom had previously had myocardial infarction. Because of the apparent effect upon the vagus nerve it was thought unwise to use it for angina pectoris until its effect was determined by clinical investigation. *Phenobarbital* can be used to control atropinelike actions associated with large doses.

It has been used in over 800 patients. Batterman and Himmelsbach<sup>5</sup> make the following statements with regard to the physical dependence upon demerol. Dependence is apt to occur only in a person who might abuse opiates but who has not had previous opiate experience. It appears to possess less liability to physical dependence than morphine. Doses maintained at less than 150 mg. every three hours seem to avoid the undesirable effects, such as cerebral irritability, and physical dependence. Effective dosage varies from 50 to 150 mg. every four hours depending on the severity of the pain encountered. Samuel Guttman<sup>6</sup> published a word of caution with regard to the use of Demerol in intracranial lesions. In seven of 20 patients there was a dangerous depression of the respiratory rate. He advises caution in the use of this drug in patients suffering with intracranial lesions. In the experience of the writer, the same caution might be asserted with regard to morphine itself.

### Dilantin Sodium in Bronchial Asthma

Dilantin sodium has been previously discussed in these columns with reference to its effectiveness in preventing epileptic seizures. Shulman<sup>7</sup> has used this drug in the prevention of bronchial asthma in seven children with good results. Realizing that asthmatic attacks are often preceded by mental or physical excitement, especially in children, it was conceived that this drug, which is used as an anticonvulsant in epilepsy, might

act as an antispasmodic in preventing attacks of bronchial asthma.

Consideration of the psychogenic aspect of asthma patients, "asthmatic personality," leads to the use of this drug much as it has been applied in epilepsy where it has proven its worth as an anticonvulsant.

Tried on seven cases of intractable severe bronchial asthma, it was concluded that it gave relief in six of seven cases. The drug must be given continuously for effectiveness. Further conclusions were that the *modus operandi* could not be determined in such a small group, but more clinical and laboratory work with this drug is indicated. Personality changes were noted. Only one case showed any toxic symptoms which cleared with withdrawal. The dosage used was arrived at by clinical trial and was found to vary from 0.1 Gm. to 0.2 Gm. (1½ to 3 grains) daily.

### **Intravenous Preparations for Rapid Digitalization**

**Ouabain and Strophanthin**—Rapid production of the digitalis effect by the use of intravenous strophanthin K and ouabain has been reported in the literature in the past year. Chávez,<sup>8</sup> Professor of Medicine of the University of Mexico, called attention to the infrequent use of ouabain in the United States and contrasted this with the more common use of ouabain or strophanthin G and strophanthin K in Mexico, Latin America, and Europe in the treatment of heart failure. It is well recognized that digitalis, ouabain, and strophanthin have similar actions in the main. Differences can be pointed out. One important difference to be considered in administering these substances is the rapid dissipation of ouabain and strophanthin K as compared with the accumulative effect of digitalis. Digitalis is preferably

administered through the oral route and often requires two or three days to reach its maximum effect, and hardly any effect is noticed short of two or three hours. On the other hand, ouabain is not at all reliable when administered by mouth; therefore, in order to secure any certain effect, it must be administered intravenously. Therapeutic action is reached in the matter of minutes, and within one hour its total effect can be noticed. After one day it has disappeared. It has no tendency to accumulate. The differences of action are probably based upon the above facts rather than that of any fundamental difference in the effects produced.

Ouabain is indicated where rapid and intensive effect is desired for relief of acute heart failure by immediate strengthening of the heart muscle. Therefore, it suggests itself in acute heart failure where fibrillation is absent and tachycardia moderate, but there may be enlargement of the heart, gallop rhythm, or alternations of the pulse and lowering of the blood pressure, with or without congestive complications. The accidents of heart failure, such as acute pulmonary edema, and paroxysmal nocturnal dyspnea are examples of conditions where ouabain may be indicated.

Among clinical conditions most likely presenting this picture are left-sided heart failure, chronic coronary insufficiency, hypertensive heart disease, and complicated syphilitic aortitis. It is considered that ouabain is indicated because of its more direct action upon the myocardium and less depressing action upon the neuromuscular mechanism of the heart. It is clear that this does not apply in conditions presenting either fibrillation or tachycardia other than for the purpose of initiating emergency control. Digitalis is well proven where fibrillation or tachycardia exist. Strophanthin K, which

is also used intravenously, and has been designated as strophanthin by the Pharmacopoeia of the United States, is an amorphous glucoside. It is also given intravenously and its excretion then is similar to ouabain in that it is totally excreted within 24 hours.

Garcia and Golden<sup>9</sup> studied the effect of this substance in 18 patients with congestive failure, including cases of arteriosclerotic heart disease, hypertensive heart disease, and a combination of syphilitic heart disease, and thyroid heart disease. Their cases seem to be similar to those for which Chávez recommended the use of ouabain. Their rationale was similar in that they recommended the immediate administration of an oral dose of digitalis which will pick up and maintain the desired effect as the strophanthin disappears. They reported no more remarkable toxic signs than those associated with ordinary effects of full digitalization with digitalis alone.

Gefter and Leaman<sup>10</sup> reported on 33 cases of rapid cardiac arrhythmias treated by means of ouabain. Their conclusions were that one intravenous dose produces the statistically significant reduction in ventricular rate and is effective in the treatment of cardiac arrhythmia of auricular origin. They point out that it is relatively ineffective in simple tachycardia when associated with infections. One oral dose of digitalis following an intravenous dose (0.5 mg.) of ouabain is effective in producing full digitalization. The dosage recommended by Chávez was 0.25 mg. per day. This dose could be repeated in one day or it may be continued daily for six days. According to the system recommended by Garcia and Goldman, they used 0.25 mg. of strophanthin K diluted with 10 cc. of physiologic saline solution injected over the period of three minutes, followed with 0.36 Gm. to 0.54 Gm. (6 to

9 gr.) of digitalis orally. These methods will probably be welcome and find more common use in this country if the contentions of the studies reported prove clinically true in wider usage.

**Lanatocide C**—While ordinarily cardiac decompensation can be treated by digitalis orally, Joseph H. Nicholson<sup>11</sup> studied the effects of lanatocide C as a means of more quickly controlling symptoms of failure. Lanatocide C (cedilanid) in doses of 1.6 mg. was determined to be the effective digitalizing dose. All these cases had rates over 120 or had auricular fibrillation, and all responded in from less than an hour to 12 hours, reducing rates to within normal limits. Here is another method by which rapid digitalis effect may be attained. One may take the choice of this method or the ones mentioned above. It must be kept in mind that those who recommend ouabain consider its transitory effect desirable, but it should also be recalled that this preparation does not have the stability of lanatocide C.

### **Lipocaiac and Fat Metabolism**

Dragstedt's presentation and study of lipocaiac offers considerable clinical interest for the immediate future. After the discovery of insulin, attempts were made to keep depancreated dogs alive by means of insulin. These dogs always died with fatty livers. MacLeod found that he could prevent the development of fatty liver by feeding fresh raw pancreas in addition to the administration of insulin. This was, he thought, due to pancreatic lipase. Hershey and Soskin later found that lecithin in doses of 10 Gm. (150 gr.) per day would have the same effect, and they attributed this to the results of lecithin. Following this, Professor Best<sup>12</sup> prevented fatty livers by adding lecithin. Breaking lecithin down, he felt it was choline which was

effective in preventing development of fatty livers. Dragstedt felt that, since only 100 Gm. of fresh pancreas was a necessary dose, this contained much less choline than used in the choline experiments, and so performed his classic experiment of fistulized pancreatic ducts in collecting large volumes of pancreatic juice. This substance had no effect on fatty livers. It still did not seem reasonable that choline was the effective substance; therefore, some other substances in the pancreas was sought. The pancreas was extracted with neutral alcohol, and the fat was extracted, which left a fat-free alcohol extract, and a fat alcohol extract. It was discovered that the fat alcohol extract was inert, and it was this extract which contained all the lecithin and choline.

However, the fat-free extract did prevent fat formation in the liver, and experiments were carried out to prove this. This substance, namely, the fat-free alcoholic extract of the pancreas, named lipocaiac, gives promise of an interesting future in clinical medicine. The writer is not certain that the actual substance is understood, and yet its effectiveness in preventing formation of fatty livers in depancreatized dogs adequately treated with insulin has been adequately substantiated. As a result of this experimental work, Dragstedt points out that there are two types of fatty livers. One is due to lack of insulin. This is associated with higher than normal blood fat and of toleration to larger doses of insulin. The second type of fatty infiltration which develops later, even with adequate use of insulin (approximately six weeks later in experimental animals), is prevented by use of lipocaiac.

The therapeutic indication seems to show the necessity for adequate control of diabetics with insulin and the possibility of lipocaiac preventing develop-

ment of fatty livers. Dragstedt has mentioned that this substance has been tried effectively in the treatment of xanthoma and further raises the question of the use of lipocaiac in the prevention of atherosclerosis.

### **Magnesium Sulfate Intravenously in Paroxysmal Tachycardia**

Boyd and Scherf<sup>13</sup> report the effectiveness of intravenous injections of 20 per cent solution of magnesium sulfate in doses of 15 to 20 cc. in the treatment of paroxysmal tachycardia. With 10 per cent solution, results are not as definite. Cases included nine cases of paroxysmal tachycardia, and one case of flutter, all of which occurred in hearts of previous organic disease. It is pointed out that at least 30 seconds should be used for the injection and yet it should not be injected too slowly. It is necessary for the drug to reach the heart in sufficient concentration to produce its specific effect.

The specific contraindications that must be guarded against are very advanced myocardial damage, marked intraventricular conduction defects, and gallop rhythm. Magnesium sulfate is known to have a depressing effect upon the central nervous system. It must also be recalled that magnesium sulfate has an accumulative effect and, if repeated frequently, particularly if the renal function is impaired, may have a tendency to accumulation. This may be sufficient to produce symptoms of magnesium poisoning. Poisoning has been known to occur from magnesium sulfate given as a cathartic. Another result which may not be suspected for its effectiveness in tachycardia could be the diuresis that it produces, thus lessening the cardiac strain. It is available in ampules of 20 per cent solution ready for injection.

## Oxygen Therapy

Under certain circumstances the problems of anoxia as it occurs in a variety of medical conditions can be treated by means of increasing the available oxygen in the inspired air. It is important to recognize the type of anoxia to be treated since all types of anoxia do not respond to this treatment. For this purpose, it is well to recall a physiological classification<sup>12</sup> of anoxia.

1. Anoxic anoxia, caused by improper ventilation from one of the following: Obstruction, paralysis, rarefied atmosphere, respiratory depression, and pulmonary inflammation states. Symptoms of anoxic anoxia include dyspnea, cyanosis, and mental disturbances as follows: Exhilaration, delirium, mania.

2. Anemic anoxia: (a) That which occurs as result of a hemorrhage or severe anemia from any cause; (b) carbon monoxide poisoning or poisoning by other substances which, when combined with hemoglobin, form stable compounds which are not broken down and the oxygen exchange is impaired.

3. Stagnant anoxia which results from circulatory failure in such conditions as cardiac decompensation and shock.

4. Histotoxic anemia which results in a failure of the tissue cells to utilize oxygen even though it is delivered, the classic examples of which are cyanide poisoning and alcoholism.

From the above classification, it is obvious that increased concentration of oxygen in the inspired air will not affect all these states; for example, severe anemias cannot carry more oxygen, regardless of the increased oxygen available, because of absence of available transport. Likewise, histotoxic anemia is not apt to benefit from additional oxygen. Certainly, peripheral cyanosis in itself is

not always an indication for oxygen therapy. One must decide that by increasing the partial pressure of oxygen in the alveolar air oxygen saturation of the arterial blood will improve. Such need arises (1) with obstruction to the passage of air to and from the lungs, or (2) with the interference with gaseous exchange in the alveoli. Examples of conditions such as these are pneumonias where large portions of lungs may be consolidated and exudates interfere with the passage of air; atelectasis, where the pulmonary area is markedly diminished; in the edema of cardiac failure; in mechanical obstruction; in bronchial asthma; in emphysema; and in carbon monoxide poisoning where a high concentration of oxygen enhances the disassociation of carbon monoxide and hemoglobin.

Oxygen may be used to advantage in diseases where local anoxia is causing symptoms, namely, coronary heart disease and coronary occlusion,<sup>14</sup> in cerebral anoxia in shock and local cerebral accidents. In most of these conditions, it is possible to provide oxygen containing 5 to 10 per cent carbon dioxide which has the property to stimulate effectively the depth of respiration. Helium and oxygen mixtures are found useful, especially in anoxia from pulmonary obstruction.

There are various methods,<sup>15</sup> each with its own particular kind of equipment, available for the therapeutic administration of oxygen. The oxygen tent, oral pharyngeal insufflation of oxygen, and the B.L.B. mask are the most important methods now in common use.

The oxygen tent mechanism varies with the manufacturer's design, and someone actually familiar with it should regulate it. Suitable instructions are usually delivered with these instruments and they are available in most metro-

politan centers. Rental from companies who specialize in this service is possible, so that oxygen may be delivered by this means in the home as well as under hospital care.

Oral nasal insufflation, where highly trained nursing care is not available, may be carried out successfully. The important factors to be considered and studied by the person who administers this are: (1) The use of the humidifier so designed that oxygen comes out in small bubbles and passes through water; (2) securing the catheter in a comfortable and effective position. In general, the deeper into the pharynx one places the catheter the greater the concentration of oxygen delivered. One method to determine the distance that the catheter is to be inserted is to measure the catheter from the tragus of the ear to the tip of the nose and make a mark upon the catheter, then insert to this mark. The tip of the catheter may be passed to just below the posterior edge of the soft palate. The amount of oxygen which the patient can tolerate and be effective by this method will usually vary from 8 to 12 liters per minute. A meter indicating the flow per minute is essential. Concentrations up to 50 per cent can be secured by this method.

Probably the most effective method yet available for securing increased oxygen concentration is the face mask of the B. L. B. type, which consists of a nasal mask attached to a small bag which provides for partial rebreathing. These masks are of two types, either the nasal or oral-nasal variety. By means of this, oxygen can be delivered to the patient up to concentrations of 100 per cent. (SEE: *Respiratory System*.) Masks lack the irritation that frequently accompanies the oral-nasal insufflation method and have the advantage of providing much greater concentrations of oxygen. Patients tend

to become accommodated to masks and can read and sleep and carry on a more comfortable and more natural bed life than with anything heretofore in common use.

A smaller oxygen tent was designed by Lambertsens and Godfrey,<sup>16</sup> and demonstrated by them at the 1943 regional meeting of the College of Physicians in Philadelphia. It is, for all practical purposes, a new method which may be predicted to be more efficient, adaptable and comfortable than the present methods. It is likely that it will not be generally available until conditions permit.

### **Papavarine Hydrochloride in Prevention of Premature Ventricular Systoles**

Papavarine is devoid of any narcotic effect and has very slight action on the central nervous system; so, in therapeutic doses, it produces neither sleep nor analgesia. However, it is kept under the control of Federal narcotic regulations because of its relationship to opium. The main action is to relieve spasm and relax smooth muscles. Rather wide clinical use has been made of this drug in recent years. Elek and Katz<sup>18</sup> discuss its use in heart disease. They mention its use in patients of the anginal syndrome but dwell more extensively upon its use in suppressing premature systoles, especially those of the ventricle where it is more successful than with auricular premature systoles. For this purpose it may be used intravenously either by dividing dose or by continuous intravenous drip diluted in saline or saline and glucose solution. Elek and Katz recommend the use of larger doses than those ordinarily used, such as 0.1 Gm. (1½ gr. orally t.i.d., and in cases of premature systoles doses up to 0.33 Gm. (5 gr.). It has a wider margin of safety than quinidine and does not depress the myocardium.



Papavarine, used to control premature ventricular systoles, offers an opportunity for the use of medication which not only relieves vascular spasm and permits increased blood flow, but by so doing prevents one of the most universally fatal cardiac arrhythmias, that of paroxysmal ventricular tachycardia. In the writer's experience there is some difference in the amount of dosage required to accomplish the result sought for. The best criterion seems to be subjective response of the patient to the medication.

One cannot help recalling, when reading the report of Elek and Katz, that when they administer this solution intravenously they use a saline solution. Saline solution itself has been recommended in vascular disease.<sup>18</sup> It may have some effect in improving the circulation in these patients.

### Plasma for the Treatment of Leg Ulcers

The treatment of leg ulcers as they occur in patients with peripheral disease by means of blood and plasma has been reported by Meyer Naide.<sup>19</sup> The first attempt of this method consisted of dropping blood taken from the patient upon the ulcer. Marked relief of pain and reduction of the surrounding reaction and finally healing rewarded this effort in many instances. Various technics were tried which consisted of concentrated plasma and whole blood applied by various methods.

Roughly, the method consists of cleansing the ulcer gently with **hydrogen peroxide**. Either blood or concentrated plasma is then dropped or run upon the surface in sufficient quantity to cover the ulcer. Time is then allowed for a dry clot to form. This clotting requires from 15 minutes to two hours, which can be shortened by using a fan. Suitable dress-

ing is then applied which remains in place from one to three days. The entire procedure is repeated as often as is necessary. It was noted by Naide that plasma clotted more rapidly than whole blood. Considering that ischemia is the probable cause for development of these ulcers, this is a very logical procedure and it is rather surprising that it has not been used previously. One cannot help imagining that it will be used as effectively in wound healing; in fact, such use of the method has already been applied.<sup>20</sup>

### Testosterone

That testicles are glands of internal secretion has been known since 1849. After this time the popular thought concerning the changes of old age in man was that signs of senility were due to failure of testicular function. Brown-Sequard administered testicular extract to himself and felt that he gained in vigor and capacity to work. The changes of senility are no longer attributed seriously to this alone, but the ability of the testicular hormone to increase vigor and capacity for work seems to find increasing support as time passes.

The general effect of testosterone as replacement therapy need not be rediscussed in this column. The metabolic effect of testosterone might be recalled. Experiments have been done to confirm the fact that as a result of administering testosterone nitrogen retention is increased, certain electrolytes are retained, and body weight increases. Muscular strength improves and exercise tolerance increases.

It has been noted that these physiological changes are similar to those accompanying precocious puberty.

As a result of this knowledge, it has been suggested and used with some success in the treatment of Cushing's syndrome. Cushing's syndrome was inter-

preted as hyperandrenocorticism leading to hypergluconeogenesis. General clinical improvement is said to have resulted and a positive nitrogen, phosphorus, calcium, and electrolyte retention followed the use of testosterone propionate. In spite of any contentions that may arise as a result of the conception mentioned above, it seems reasonably well established that testosterone can increase the metabolism and retention of protein and electrolytes.

Davidoff and Goodstone<sup>21</sup> recommended the use of testosterone propionate in the differentiation from other organic conditions and the treatment of involutional psychosis in the male. Their dosages began with 25 mg. three times weekly and were gradually reduced to much smaller quantities. Successful results occurred in about 46 per cent of the patients treated. One of the uses of this treatment was to differentiate the type and severity of the psychosis encountered.

Several sources have studied and recommended the use of testosterone propionate in the treatment of angina pectoris.<sup>22-24</sup> Exercise tolerance in four subjects was reported as increased. Severity and duration of attacks were diminished. In another series, controls were run upon well selected cases. A number of the cases showed relatively definite improvement, supporting the claims of other writers.

It is to be noted that testosterone here was not used for the immediate relief of anginal pain but rather more with a view of rehabilitation of the patient. It is interesting that Thomas McGavack<sup>24</sup> reports upon anginal pain in the male climacterium. In this instance, the pain did not respond to sedatives and vasodilator drugs. Symptoms, such as impotence, easy tiring, myalgia and arthralgia, insomnia, and vasomotor disturbances were interpreted as evidence for

changing testicular function. The fact that these patients responded to the administration of testosterone, either by pellet or testosterone propionate injections or methyl testosterone by mouth, lead to the conclusions that they differed from other forms of angina which were relieved by vasodilators and sedative drugs. This raises the question as to whether all cases of angina respond, or whether there is the true differentiation, as McGavack has pointed out, and are these cases from the male climacteric groups alone, those which give favorable results.

### Thiouracil

**Hyperthyroidism** — Astwood<sup>25</sup> reports that the administration of thiourea in doses of 1 to 2 Gm. (15 to 30 gr.) daily, or of thiouracil in 0.2 to 1 Gm. (3 to 15 gr.) daily to hyperthyroid persons resulted in the relief of symptoms and return to normal. Astwood reports three cases effectively treated with both of these substances, and found complete remission of symptoms of hyperthyroidism, but also observed that it was necessary to continue the treatment in order to maintain the desirable effect.

The action of thiouracil from present information seems to result from the inhibiting of the formation of thyroxin. This was felt to be due to effect upon the gland itself because it has been found that the administration of thiourea does not inhibit the effect of thyroxin or thyroid when given simultaneously. This has been confirmed both in animal experiments (McKenzie and McKenzie),<sup>26</sup> and in human experiments (Astwood, Sullivan, Bissett, and Tyslowitz).<sup>27</sup>

It was further found that the thyroid gland could be stimulated to become hyperplastic when thyrotropic hormone was administered to a patient, but that with the coincident administration of 1 Gm. (15 gr.) of thiouracil daily for

0 days the basal metabolic rate showed no response. In these respects the action of thiouracil somewhat resembles what occurs with the administration of cyanates.<sup>28</sup> Here the thyroid gland is hyperplastic but hypofunctioning.

The length of time that is necessary to continue this treatment has not been discovered. It would seem that several possibilities might occur. The drug may be given permanently to obtain relief continuously. Against this is the knowledge that what occurs with the other similarly acting substances, namely thiocyanates, may also occur in this instance, producing hyperplastic gland with myxedema. It may be necessary to administer the drug intermittently, but this would not seem to offer a very satisfactory result, and for the average patient it hardly provides a satisfactory state of affairs as far as control is concerned. The patients themselves are unable to tell soon enough when toxic symptoms are appearing or disappearing; therefore, they would require more supervision than ordinarily provided.

There still remains the possibility that this drug will ultimately not prove satisfactory. Another thought which occurs is the fact that some of the hyperplastic changes which occur with the administration of sulfonamide, thiourea, and thiourea derivatives can be prevented by the administration of thyroid. If this proves a practical solution, that is, the administration of thiouracil simultaneously with small amounts of thyroid, it amounts practically from a physiological viewpoint to completely shunting thyroid or thyroidectomy by medical means.

### The Metric System and Prescription Writing<sup>30</sup>

Concerted efforts are being made to encourage universal use of the metric system in place of the old and traditional

system of measures and weights in prescription writing. Conversion tables will probably be published widely. This effort is not new but there is promise that more will be accomplished and general use of metric, or centimeter-gram-second, system in the United States will be accomplished. Some of the reasons mentioned in the report by the Council on Pharmacy and Chemistry of the American Medical Association for this effort are: First, the universal uses of the metric system in scientific work; second, to simplify; third, prevention of accidents in dosage due to confusion between the two systems now in use. The Council requests the co-operation of teachers, students, and medical firms in using the metric system.

For this purpose, conversion tables are listed as follows:

1 milligram (mg.)	..... =	0.015 gr.
1 gram (Gm.)	..... =	15.4 gr.
1 gram	..... =	0.25 dr.
1 gram	..... =	0.03 oz.
1 kilogram (kg.)	..... =	2.2 lbs.
1 kilogram	..... =	0.16 st.
1 grain (gr.)	..... =	64.8 mg.
1 grain	..... =	0.06 Gm.
1 drachm (dr.)	.. = 60 gr. =	3.9 Gm.
1 ounce (oz.)	.... = 8 dr. =	31.1 Gm.
1 pound (lb.)	.... = 16 oz. =	0.45 kg.
1 stone (st.)	.... = 14 lbs. =	6.35 kg.
1 cubic centimeter (cc.)	... =	16.9 min.
1 cubic centimeter	..... =	0.28 fl. dr.
1 cubic centimeter	..... =	0.035 fl. oz.
1 liter	..... =	35.2 fl. oz.
1 liter	..... =	1.76 pints
1 minim (min.)	..... =	0.058 cc.
1 fluidrachm		
(fl. dr.)	... = 60 min. =	3.6 cc.
1 fluidounce		
(fl. oz.)	... = 8 fl. dr. =	28.4 cc.
1 pint	..... = 20 fl. oz. =	0.57 liter
1 pint	..... =	568.2 cc.

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## UROLOGY

ELMER HESS, M.D.

## ANESTHESIA

**Intracain** (Squibb) has been shown experimentally to possess advantages as a surface anesthetic over other local agents. Belt and Bavetta have used intracain over a period of two years for approximately 13,200 cystoscopies and 5280 urethral dilatations without a single toxic reaction. They use it as an anesthetic agent in the urethra and bladder prior to cystoscopy or dilatation with sound or Kollmann dilator. Its chief virtue, in addition to the low toxicity, is the duration of anesthesia which contributes much to the postinstrumental comfort of the ambulatory patient. It is also of value in the treatment of some painful urinary symptoms. A 2 per cent solution is used and the amount injected into

the urethra and bladder for cystoscopy is usually 5 cc. and 10 to 20 cc. if the instrumental intervention is apt to be especially painful.

**Intracain in oil** has relieved the symptoms of many types of acute and chronic cases of cystitis, as well as the distressing symptoms in various types of prostatitis. It relieves bladder spasms frequently associated with these conditions. A marked reduction in frequency, burning, urgency, and other distressing symptoms has been noted. In the presence of bladder spasm, 20 to 30 cc. of intracain in oil is instilled into the bladder through a catheter, frequently relieving the condition without any untoward reaction on the part of the patient.<sup>1</sup>

## BLADDER

### Rupture of the Bladder, Urethra, and Penis

During the study of 147 instances of rupture of the urinary bladder over a ten-year period, there was such a high attendant mortality that a careful analysis of these cases has been made and the following observations recorded.

One hundred and two cases were due to external trauma, 40 to transurethral instrumentation, and five were due to spontaneous rupture. The external traumatic agents responsible were moving vehicles, 73; falls of various types, 11; gunshot wounds, 9; kicks or blows, 7; stab wounds, 1, and sitting on a sharp object, 1. Twenty-eight and five-tenths per cent of the patients were intoxicated or had been drinking prior to the accident. Twenty-three of the cases due to transurethral instrumentation were incidental to transurethral prostatectomy. During this period there were 1629 transurethral prostatectomies and the incidence of accident occurred in 1.4 per cent of the cases. Catheterization preceded seven instances of rupture of the bladder and cystoscopy accounted for four, fulguration or biopsy of the bladder for four, and lithopaxy and Pezzar catheters for one, spontaneous rupture occurred in four cases of carcinoma, and the fifth had no history of trauma.

The age group ranged from 5 to 89. There were 90 males in the series and 57 females. Pain, shock, hematuria, retention of urine, and skeletal injuries were the symptoms. The diagnosis was established by these symptoms and the history of injury, physical findings, roentgenographic evidence, urography, surgical exploration, and autopsy. Urography was the most important single diagnostic procedure.

Sixty-one and two-tenths per cent of the cases ruptured extraperitoneally. In 102 cases, 72 patients sustained fractures of the pelvis and in a large percentage of the cases where the pelvis was not fractured, the bladder ruptured intraperitoneally. One hundred and twenty-six of the 147 patients were operated upon and, of the remaining 21 patients, 19 died. Suprapubic cystostomy was performed in 64; suprapubic cystostomy and repair in 49; vesical repair and indwelling catheter in 11 (4 of these died), and drainage of the prevesical space and indwelling catheter in 2. The surgical mortality was 36.5 per cent. The total mortality was 44.2 per cent.

It is a well recognized fact that the earlier these cases are operated upon, the lower will be the mortality. This high mortality, in all probability, can be explained by the fact that from the time of injury until operation, the average was 19.8 hours, while the average time from admission to the hospital until operation was 11.3 hours. This delay in surgery has been attributed to the fact that many of these cases were admitted to the orthopedic, neurosurgical, or general surgical services before the rupture was suspected. Important considerations in the treatment of all cases of rupture of the urinary bladder are those things which are done to offset shock, early diagnosis, prompt surgical exploration, and suprapubic drainage. These cases must be handled immediately. They must have external heat, blood grouping, intravenous solutions, physical examination, plain roentgenograms of the area from the ribs to the pelvis, catheterization, contrast cystograms, and surgery. Cystoscopy should seldom, if ever, be done and only adds to the trauma already existing. If there is any suspicion of other visceral damage at the time of operation, the peri-

toneum should be opened and explored. Death may be due, very often, to associated pathology, such as multiple fractures, traumatized intraperitoneal viscera, and shock. Very often other lesions are of such seriousness as to offset the prompt, energetic treatment of a bladder rupture by surgical measures.<sup>2</sup>

### Tumors

Many cases of papillomatous carcinoma of the urinary bladder are undoubtedly due to carcinogenic substances that may be classified as hereditary, chemical, mechanical, thermal, and actinic. In the last group are those whose activity may be due to x-ray, ultraviolet light, and sunlight. It is possible that these substances produce cancer by destroying the cancer resistance mechanism in the cell. It is a well recognized fact that various chemicals used in industry produce bladder cancer. These are numerous. Anilin dye workers are noted for the frequency with which they develop bladder cancer. It is conceivable that many proprietary remedies, and particularly cosmetics, if used over long periods of time may produce the disease. Some of these carcinogenic substances are coal tar and tar-distillation products, shale oil, various crude mineral oils, paraffin, chromium, radioactive substances, betanaphthylamine, and under suspicion are nickel, zinc chloride, asbestos, potassium nitrate and silica, iron and copper dust. Chemicals produced by the individual within his own body also definitely fall in the carcinogenic class. They are acetylcholine, vitamins, and estrus-producing substances.<sup>3</sup>

All of these things must be taken into consideration when a patient with painless hematuria presents himself or herself to the physician, and when after cystoscopy a bladder tumor or tumors

are found. The diagnosis of the disease is comparatively simple. Any patient presenting the single symptom complex of painless urinary bleeding demands an immediate urological study. If tumor or tumors are found, an intravenous or retrograde urogram is immediately indicated to ascertain the condition of the ureters, pelvis, and kidneys. If then the diagnosis of bladder neoplasm is made, the treatment must be designed to fit the situation found. **X-ray therapy** has a distinct place in this field, but the two things that must be immediately evaluated are, first, is the tumor composed of cells that are radiosensitive, and second, what shall be the technic of the administration of the roentgen application. With all of our present experience it is impossible to state which bladder tumor will respond favorably and how favorably it will respond to any given x-ray therapy.

On several occasions, the writer has turned over for roentgen therapy bladder tumors that for one reason or another he did not feel like subjecting to any other therapy, not so much expecting to cure the condition but in an attempt to give a hopeless patient some hope. Surprisingly enough, quite a goodly number have been apparently cured for long periods of time, many such patients (particularly elderly people) dying from some other cause. For just such reasons as this, no case should be completely labeled hopeless to the patient, no matter what the prognostic opinion of the urologist may be.

Radiosensitive tumors, therefore, are those which respond favorably or show complete local regressions after a total dosage of 2500 R., while radioresponsive tumors require for the same results 2500 to 5000 R. Tumors that do not respond favorably to 5000 R. are considered radioresistant. This is a fairly good way

to classify tumors of the bladder and while, not totally accurate, gives the roentgenologist and urologist a definite rule which may be fairly well applied clinically.

Squamous cell tumors, as a rule, are radioresistant, while the degree of sensitivity of the papillary tumors is often based upon the degree of undifferentiation of the tumor cells. Therefore, no patient should be subjected to x-ray therapy until a complete urological examination is made, including biopsy.

In a series of 160 patients with carcinoma of the bladder treated by external radiation from January 1, 1938, to December 31, 1941, Herger and Sauer<sup>4</sup> report that 25 patients had papillary carcinomas, 91 papillary infiltrating carcinomas, and the remaining 44 had solid infiltrating carcinoma. If 200 K.V. radiation was given, 2, 3, and 4 fields were treated with a daily increment varying from 100 to 400 r. If supervoltage radiation was employed, it was given through 3 or 4 portals, with a daily increment from 100 to 300 r. Satisfactory results were obtained in more than 50 per cent of the patients with papillary and papillary infiltrating carcinomas. In 13 cases the tumor disappeared entirely after external radiation alone. In 44 patients, marked regression in size and number of the tumor growths was obtained, rendering the tumor suitable for subsequent transurethral treatment, while in 24 cases the regression was only temporary.

In 35 patients with papillary carcinoma, no results were obtained, while in the 44 cases of infiltrating carcinoma a favorable response was obtained in only one case. In the vast majority of cases of tumor, transurethral fulguration, with the implantation of radon seeds, is an essential adjunct and may be the procedure before external radiation is tried; com-

bination of fulguration, radium, and x-ray may be advisable, the experience of the operator being the yardstick for any kind of therapy.

In the solid infiltrating tumors of the bladder none of these methods will suffice except for purposes of palliation. It is in these cases that *bilateral transplantation of the ureters, with total cystectomy*, must be considered if the patient is to have a chance for cure. However, it must be remembered that if the cancer has spread beyond the confines of the bladder wall this therapy will not cure.

When this diagnosis is made it is essential, under anesthesia, to do a recto-abdominal palpation. Infiltration of the bladder muscles is felt on such examination as a hard mass in the bladder wall, and its size may be estimated in three dimensions and it may be very much larger than the cystoscope seemed to reveal. The only cases suitable for ureteral transplantation and total cystectomy are those where the bladder mass is freely movable. This operation of transplantation of the ureters, with total cystectomy, is not new.<sup>5</sup>

However, since the operation has been made an extraperitoneal one the mortality has dropped to almost zero. This requires, of course, three incisions; one each for the transplantation of each ureter and a midline incision for the cystectomy. It is believed that total cystectomy can now be done with comparative safety after the ureters are successfully transplanted to the bowel. If the ureters are dilated and are not of normal size, however, they should not be transplanted to the bowel but should be brought to the surface of the abdomen. This should only be done when transplantation to the bowel is considered impossible or not feasible.



## ENDOCRINE DIAGNOSIS AND TREATMENT

The urologist is constantly confronted with both children and adults who are sent to him for endocrine diagnosis and treatment. It is, therefore, necessary for him to avoid errors in diagnosis as well as treatment. Quite frequently all of the errors that are made on B.M.R. readings concern the preparation of the patient for the tests and most of these errors are plus errors. There are a number of nonendocrine conditions which are accompanied by minus readings. Hypopituitarism and hypoadrenia show almost as low readings as does hypothyroidism. A diagnosis of the latter should not be made unless it is well supported by the clinical history and other findings.

The victim of hypothyroidism is sensitive to cold and needs heat. In hypoadrenia, there is just as much sensitiveness to cold as there is to heat. Exposure to high temperatures may provoke a crisis in Addison's disease. Hypopituitarism is not apt to be affected by extremes of temperature. The hypothyroid is relieved by adequate doses of *thyroid* and it is customary to begin with 0.065 Gm. (1 gr.) per day for adults. The same amount aggravates the symptoms of the patient with hypoadrenia but where there is also a concomitant thyroid deficiency, it may improve it.

The subcutaneous injection of 0.5 cc. (8 minims) of *anterior pituitary extract* will give relief in cases of hypopituitarism, while the administration of 0.3 Gm. (5 gr.) t.i.d. of *desiccated suprarenal* or of preparations of *adrenal cortex* for one week will produce some relief in the hypoadrenia.

In those nervous states which are attributed to other causes than thyroid disturbances it is necessary to study the pituitary, adrenal, and gonadal status.

In obese patients with combined thyroid and pituitary deficiencies, an elevated B.M.R., and tachycardia, cautious administration of thyroid will sometimes reduce the tachycardia and obesity.

X-ray films of the sella in disturbances of the pituitary, excepting in tumor, are of little value. However, there are many obese children with hypogonadism who should receive treatment. Many of these children need thyroid. It is advisable to begin with 0.016 Gm. ( $\frac{1}{4}$  gr.) per day and increase by 0.016 Gm. ( $\frac{1}{4}$  gr.) not oftener than once a week. Most of these youngsters need *posterior lobe extract*, 0.006 to 0.013 Gm. ( $\frac{1}{10}$  to  $\frac{1}{5}$  gr.) in enteric coated capsules three times a day. It may be given subcutaneously in doses just short of the amount which will produce gastrointestinal symptoms.

Care must be taken not to label as psychoneurotic patients who fall under the pathological heading of endocrinopathies. Medication must not be given in large or too frequent dosage.

Anterior pituitary extract and *testosterone propionate* should not be given in large doses in the climacteric, but in hypogonadism, doses of gonadotropins may be given as high as 300 units daily or on alternate days. It must be kept in mind that doses of 50 to 100 units twice a week are usually sufficient. The danger of provoking hypergonadism, of unduly hastening closure of the epiphyseal lines, or of producing glycosuria must always be kept in mind in treating young adults.<sup>6</sup>

## GONORRHEA

**Gonorrheal Vaginitis** — The treatment of this disease, if attempted at home, necessitates an intelligent parent coöperating fully with a social worker and/or a competent, well-trained visiting nurse. It is necessary to educate these families on sex hygiene and venereal

prophylaxis and instruct them to watch for and prevent dangerous contacts. Anything in the home that does not educate and improve the socio-economic standards is a distinct handicap in the treatment and prevents cure as well as leads to a possible spread of the disease. The source of the infection may be in the family; it may be at school, but whatever the source, it should be found and eradicated. This is much simpler in an organized clinic, particularly if the patient must be treated at home. (If suspicious contacts refuse examination or treatment, police or court intervention is absolutely essential.) All cases of gonorrheal vaginitis should be barred from school, but where many children are involved, separate teaching should be encouraged for these youngsters.

**Examination**—Before specimens for slide or culture are taken, all accumulated secretions should be removed from the urethra, vagina, cervix, and anorectal regions. The smear should be spread as thin as possible so as not to cause imperfect staining of the diplococci. Approximately 10 per cent of these infected children present anorectal involvement and in all cases of gonorrhea in the female the anorectal area should be cultured because reinfection of the vagina may be due to an unrecognized anorectal infection.

**Prognosis**—Gonorrhea in women is a curable disease and in children the vast majority of the cases are likewise curable. It may require six months to two years to cure juvenile gonorrheal vaginitis and this must be remembered.

**Treatment**—This must be individualized, whether the patient is treated at home or at the hospital. A favorite treatment is the so-called alternating or rotating treatment. The same drug should not be used locally each day because of the ability of the tissue cells

and microorganisms to accommodate themselves to a certain drug. Therefore, the four types of drugs which are used locally and rotated are *silver*, *heat*, *estrogens*, and *sulfonamides*.

Some men have advocated the treatment of gonorrheal vaginitis by estrogenic substances, and it has been found that while this substance in some respects increases the potency of other drugs used in conjunction with them, still there is much experimental evidence to prove that estrogens alone are not curative.

In a large percentage of cases, it has been found that at least 2400 to 4800 International Units of natural estrogenic substance used daily in suppository did some good, but great care must be exercised that secondary sex characteristics do not develop too early. *Stilbestrol* proved to be very much better than natural estrogenic substances and effective progress seemed to be made if 1 mg. per day by mouth was used. However, 2 mg. per day by mouth should never be exceeded. This latter dosage also caused secondary sex characteristics to develop which is, of course, an undesirable situation.

At the present time a new synthetic estrogenic drug, *octifollin*, has been administered orally or by suppository in a large number of cases. This seems to be an improvement over stilbestrol. There are no reactions from the use of the drug and no secondary sex characteristics have appeared even when the drug has been given for four or more weeks. The drug is only half as strong as stilbestrol and twice the amount must be given to attain similar results. All of these drugs, apparently, must be administered with great caution before the age of puberty.

In the minds of most workers, it must be again emphasized that estrogens,

natural or synthetic, alone are not the answer in the treatment of gonorrheal vaginitis. *Sulfathiazole* with properly regulated dosage and a safeguarded patient is a great help. Gram-negative diplococci seem to acquire a resistance to the drug if continued for any great length of time; but in both women and children its early use establishes a decided progress in the treatment of the disease. Local applications of *sulfanilamide*, *sulfapyridine*, and *sulfathiazole*, either alone or in combination with various hormones in suppository form, have not been of much value. The combination of estrogens, sulfathiazole, and local treatment will usually shorten the period before the first negative slide.

It must be remembered that there is no specific cure for gonorrhea in females, that any one of a number of methods is of value, and no case should be discharged as cured on the strength of a few negative smears.

To summarize, the treatment of gonorrheal vaginitis in children depends upon rigid attention to details of diagnosis and therapy, accurate laboratory findings, efficient nursing care in hospital or home, investigation, social service coöperation, and sufficient contact with the patient after a negative phase is established to safeguard the permanency of the cure.

The very best gonococcicide is silver and the local alternating method of treatment using some potent form of silver in the rotation, is far superior to the continued use of any drug. Heat may be successfully added. Intercurrent local conditions, constitutional or remote deficiencies, must be overcome. The prognosis is good under such a regime.<sup>7</sup>

There are a number of cases of gonorrhea which have become sulfonamide-fast in spite of the fact that the sulfa group does cure a large percentage of cases if

properly used. However, when a case is isolated and in which the infection has become resistant to adequate sulfonamide treatment, the new drug *penicillin* seems to have a special indication. Because of the limited amounts of this drug which are available, only a small series of cases which did not respond to therapy were treated with the drug, with excellent results. Penicillin is antibacterial for the gonococcus and is excreted rapidly in the urine.

Approximately one-third to one-half of the penicillin is excreted through the urinary apparatus. The high degree of solubility of the material permits it to reach involved tissues easily. It is therefore ideal in infections of this type. It is used intravenously. The largest amount of penicillin administered over a 24-hour period was 32,000 Oxford units. Half of the 24-hour dose is dissolved in one liter of isotonic solution of sodium chloride. If this is undesirable, it may be administered in a 5 per cent solution of dextrose in triple distilled water without any loss of activity. Initially between 100 and 200 cc. of the material are administered intravenously at a fairly rapid rate, then the rate of injection is regulated to between 30 and 40 drops per minute. The second liter may be attached to the continuous intravenous system eight to ten hours later. Repeated venipunctures may be avoided by allowing dextrose to drip in slowly during the intervals in which penicillin is not being administered. Pyrogen-free penicillin causes no toxic reactions but it must be made up fresh.

Most of the patients were cured in 3½ days with this therapy, and it is interesting to note that negative bacterial cultures were obtained sometime between 17 and 48 hours after the institution of the therapy.

At the present time it is very difficult to get the drug and its general use for the treatment of Neisserian infections and a study of the results will not be possible until after the war, but it seems probable that the use of penicillin may help to solve the problem of gonorrhea, not only in the male but in the female and in gonorrheal vaginitis.<sup>8</sup>

### PENICILLIN

This drug was found to be most effective in the treatment of staphylococcic, gonococcic, pneumococcic, and hemolytic streptococcus infections. Its effect on sulfonamide-resistant gonococcic infections was particularly striking, patients becoming symptom-free and bacteriologically negative within 9 to 48 hours after total dosages ranging from 100,000 to 160,000 Oxford units were given.

The results in patients with bacterial endocarditis, however, had been disappointing. From 240,000 to 1,760,000 units administered over a period of from 9 to 26 days in general produced no appreciable effect on the course of the disease.

Penicillin is relatively low in toxicity. The following reactions were noted in 500 cases: Five had fever; 12 had chills and fever; 19 had local thrombophlebitis; 14 had urticaria; 5 had muscular tenderness at the site of injection; 10 had headaches with flushing of the face; 2 had tingling in the testes, and 2 had pain in the muscles. All of these symptoms were transitory and disappeared very quickly and were considered due to impurities. Penicillin that has the pyogenes removed has not caused these reactions.

Staphylococci, pneumococci, and hemolytic streptococci can be made penicillin-resistant. Such resistant strains, however, seem to remain susceptible to the sulfonamides.

Herrell and Nichols found that the calcium salt of penicillin is more stable and easier to handle because it is non-hygroscopic. They administered the calcium derivatives by intravenous drip and noticed no untoward reactions in daily doses up to 44,000 Oxford units over periods of 3 to 14 days.<sup>9</sup>

The use of penicillin in unhealed compound fractures, osteomyelitis, and wounds with long established infections have given such encouraging results that further studies concerning the use of the drug in these conditions and in the venereal field have been planned in ten army hospitals. It will be interesting to note the effects of the drug as a prophylactic agent against the formation of renal stones in those cases where it has been used to control infections in compound fractures and osteomyelitis.<sup>10</sup>

The sodium salt of penicillin may be given by the oral, intraduodenal, rectal, intravenous, subcutaneous, intramuscular, intrapleural, intraarticular, and intrabursal routes. By mouth and rectum the drug seems to be poorly absorbed, while absorption and excretion of the drug is very rapid after intramuscular injection or very slow after subcutaneous injections. The choice of administration is intravenously or intramuscularly.<sup>11</sup>

It has been found that the maximum excretion is through the urine but that if 30 cc. of *Diodrast* are given just prior to the penicillin, the *Diodrast* seems to block the excretion of penicillin without having any effect on its bactericidal properties: The average excretion of penicillin during the first four hours after injection was 57.2 per cent but after the *Diodrast*-penicillin combination, only 32 per cent was excreted in 24 hours.<sup>12</sup>

### Penicillin in Syphilis

J. F. Mahoney and R. C. Arnold treated four well-controlled cases of early

syphilis with penicillin. Twenty-five thousand Oxford units were given intramuscularly every four hours for eight days, totaling 1,200,000 units. Dark field examination of the syphilitic lesions became negative seven hours after treatment and the patients became serologically negative.

Dr. Mahoney does not wish to be quoted until after a two-year careful study of the treatment of syphilis by penicillin has been made. It is reported because of its possibilities.

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## KIDNEY

**Hypertension** — All hypertensive cases should have the benefit of a complete urological survey by a competent urologist. There are those who believe that the vast majority of cases of hypertension (malignant, essential) are caused by renal lesions. Urologists and internists throughout the country should become stimulated to more thorough cooperation as a result of the reports now so frequent in the literature.

The kidney, ordinarily, is a silent organ and this fact must always be kept in mind. Repeated attacks of pyelonephritis occur without any subjective symptomatology and are only discovered by accident when a hypertension is uncovered during a routine physical examination. Many of these patients will show almost normal urinary findings during the intervals between the attacks and often during the acute exacerbation. Many cases of unilateral renal disease will cause hypertension which is promptly relieved upon removal of, or when proper treatment is applied to, the offending organ. The literature is recording these experiences with greater frequency.

Hypertrophy and cancer of the prostate are being relieved surgically in many cases with a concomitant fall in exces-

sive blood pressures. As a result of these observations, unfortunately, many kidneys with pathology are going to be sacrificed with the hope that an existing essential or malignant hypertension problem will be solved. This is, of course, not borne out by the experience of many authoritative students of hypertension.

The author has noticed that many cases of urinary obstructive disease, with high blood pressure, are definitely improved following the relief of the obstruction, but he has been unable by any known methods of examination so far developed to say before he relieves the obstruction that the hypertension will or will not be improved. Occasionally, where it is found that there is an atrophic kidney due to repeated attacks of pyelonephritis on one side and a normal or hypertrophied organ on the other, the hypertension will be relieved by the removal of the atrophic organ. Here, again, there is no means as yet at our disposal to prognosticate correctly concerning the hypertension. Operative attack on both kidneys at present is completely unjustified by any information which has been supplied, either from clinical experience or the experimental laboratory. At one time, both bilateral decapsulation of the kidney and bilateral renal sympathectomy seemed to give some hope in hypertension. Both of these surgical procedures are absolutely worthless in the treatment of hypertensive disease of renal origin.

Further reports by Page and other experimenters concerning the use of renal extracts in these conditions are anxiously awaited, but as yet these extracts are too expensive, as well as too experimental, to be part and parcel of the armamentarium of the clinician called upon to treat this disease.

Four cases of unilateral renal disease with hypertension have been reported,

all of which were relieved following **removal of the diseased kidney**. One was a case of perinephritis with perinephric adhesions following a pyelolithotomy; two were cases of hydronephrosis, and the fourth case was a definite pyelonephritis. All of these patients showed arteriolarsclerosis in the removed kidney, and it was believed that the hypertension was directly caused by the unilateral pathology.<sup>13</sup>

Fifty-five patients with advanced hypertension were studied, who presented no urological symptoms. Careful history revealed a high percentage of bed wetters and of chills and fever during childhood. Twenty-six out of the 33 women had had a toxemia of pregnancy or a pelvic operation, or both. On examination, 54.4 per cent of the whole group were found to have obstructive lesions of the lower urinary tract, while 60 per cent showed various changes in the upper tract which were due to back pressure. Renal calculi, ureteral calculi, renal cyst, polycystic disease, duplication of ureters and pelves, and ptosis of one or both kidneys were also found.<sup>14</sup>

It must be emphasized that retrograde cystoscopic examinations are indicated in these cases and that the reports and evaluations of urinary tract conditions must not be based alone on intravenous pyelography.

Some interesting experimental results are reported in hypertensive disease. As is well known, permanent high blood pressure can be produced by obstructing the blood supply to one kidney. Like the results in man, half of the animals showed no lowering of the blood pressure and only a small percentage were cured of their hypertension upon removal of the organ. However, if the affected kidney had become completely devoid of a blood supply, its removal was a useless procedure. The greatest success follow-

ing nephrectomy was in those whose hypertension was of short duration. It is noted that within the limits of the experiments, the severity of the hypertension was not of importance in determining the end result.<sup>15</sup>

To sum up, then, our knowledge of the cause of hypertension and its therapy, it may be said that many of these cases are of renal origin and that there is at present no positive surgical approach. The clinician is only justified in operating after a careful urological examination if a surgical lesion can be found and actually demonstrated. The result of this therapy may prove beneficial to the hypertension; it may completely cure it, but the chances are that the hypertension will not be influenced one way or the other and certainly, unless pathology can be positively identified, urological surgery is at present never indicated.

**Reactions to Sulfa Drugs**—Due to the extensive use of the sulfa drugs, a warning that there may be serious toxic and renal reactions is very important. In contradistinction to *sulfathiazole* and *sulfapyridine*, *sulfadiazine* is considered by many men the ideal drug of this group in the treatment of various types of infection. In spite of its apparent safety, there are toxic reactions to the drug, some of which are very severe.

During the past six months at Bellevue Hospital, sulfadiazine has been used extensively in the treatment of pneumonia. Thirty-five patients were observed who had crystals of acetyl-sulfadiazine in the urine, plus an occasional mild colic and microscopic hematuria. There were 10 patients who were very seriously ill, 3 of them dying. A study of fluid intake and urinary output in these 10 cases with severe reactions was not sufficiently studied. It is considered of vital importance to force fluids to a minimum



of 2000 cc. throughout the administration of the drug, and to note carefully the urinary output. If this drops to 800 cc. or less, it is a decided danger sign. The recorded blood sulfadiazine levels varied from 12.2 to 32.2 mg. The proper way to treat these cases is to stop the drug at once. Fluids should be forced and, in the case of complete anuria, both ureters should be catheterized, the catheters left *in situ* and irrigated every hour or two for several days. In some of these severe cases enough damage already may have been done to the renal tubules so that a fatal outcome will result, and while death cannot be directly attributed in these 3 cases to sulfadiazine *per se*, it is necessary that patients receiving large doses of the drug should receive at least 2000 cc. of fluid daily, with constant attention directed to the urinary output, the blood level of sulfadiazine, and the nonprotein nitrogen.<sup>16</sup>

Added to these observations is the study of a series of cases who were under large dosage of the drug, where it has been observed that the alkalinity of the urine has a great deal to do with the crystallization of the drug in the urinary tract. The addition of sufficient bicarbonate of soda to render the pH of the urine 7.5 or higher is absolutely necessary. This calls for the administration of the bicarbonate, 10 to 20 Gm. ( $2\frac{1}{2}$  to 5  $\bar{3}$ ) daily, while the drug is being exhibited. If the alkalinity of the urine is kept high, there will be less tendency for the drug to crystalize in the urinary tract. If the pH falls below 7.5, increasing the dosage of the bicarbonate will help to redissolve the drugs, thus preventing stasis, obstruction, and permanent renal damage.<sup>17</sup>

**Treatment of Renal Calculi**—The *surgical treatment* of kidney, ureteral, and bladder stones has been pretty thor-

oughly standardized. Much work has been done on the metabolism, bacteriology, and chemistry of urinary calculi, and it has been found that the prevention of the recurrence of calculi following operations requires the isolation of the infecting organism if present, the correction of stasis, and an investigation of metabolic errors, such as cystinuria, hyperparathyroidism, and excessive calculinuria. That dietary regulation is necessary in uric acid, oxalate, and phosphate metabolism has been proven. Vitamins A, B, C, and D, while thought to have something to do with the formation of stones, have not been proven as positive clinical factors. The elimination of all foci of infection is necessary.

Higgins has shown that certain types of renal stones are definitely influenced by an acid or alkaline ash diet and he advocates large doses of *Vitamin A*. Urea-splitting organisms which prevent high acidification of the urine are sometimes responsible for incrustated lesions of the bladder. *Phosphoric acid*, 1 per cent, has been used to lavage the kidney where phosphatic stones and phosphatic debris are present and has been used in the incrustated cystitis that goes with ulcer, tumor, and carcinoma. Very often bladder tumors which have been treated by x-ray and radiation therapy leave the patient as miserable after therapy as before. This is due to late radium reactions complicated by phosphatic incrustations. Many types of treatment have been advocated for the relief of the patients suffering with this condition.<sup>18</sup>

Experiments carried out by Suby, Suby, and Allbright have brought the problem of dissolving inorganic stones in the urinary tract considerably nearer to its solution by the local application, without surgery, of the so-called "*Solution G*," the formula for which is:



<i>R Citric acid</i>	
(monohydrous) .	32.2 Gm. (8.35)
<i>Magn. oxide</i>	
(anhydrous) ...	3.8 Gm. (15)
<i>Sod. carb.</i>	
(anhydrous) ...	4.4 Gm. (1.155)
<i>Distilled water ad..</i>	1000.0 cc. (34 fl. 3)

Sauer and Neter,<sup>19</sup> working under C. C. Herger, subjected a large series of patients with late radium reactions, complicated by the formation of alkaline incrustations at the site of the lesions, to this therapy. All of these cases were treated by continuous drip irrigation of the bladder with Solution G, with the disappearance of the incrustations within one to three weeks, followed by healing of the ulcerations. The urine, persistently alkaline before irrigation, became and remained acid following treatment. An attempt was made to prove whether or not the improvement of the urinary infection was due to dissolution of the incrustations alone or also to a direct antimicrobial action of Solution G. It was discovered that such a well tolerated solution of low pH such as Solution G had definite urinary antiseptic properties. All tests performed seemed to prove this fact.

A case of a large vesical phosphatic calculus, measuring 5.5 by 4.0 cm., which was dissolved by irrigations with Solution G has been reported. However, it must be remembered that in the treatment of urinary calculi, infection and stasis must be corrected, even if this new dissolving agent is used.<sup>20</sup>

The editor has had the experience in two cases where, following nephrostomy, soft phosphatic stones formed in the renal pelvis soon after operation. Continuous irrigation of the renal pelvis with a two-way catheter or by continuous irrigation through the nephrostomy tubes with Solution G have been so efficient that postoperatively this solution is be-

ing used routinely as an irrigation where there is x-ray or other evidence of incrustations by the phosphates on the drainage tubes. Plastic operations upon the renal pelvis, which require the use of the splinting catheter from four to six weeks, often are complicated by phosphatic incrustations on the catheters or drainage tubes. These may be kept clean by the daily use of Solution G and by continuous irrigation with Solution G if intermittent irrigations with the solution do not suffice. The author's experiences with incrustated cystitis and with the incrustated roentgen-ray and radium ulcerations have been as satisfactory as those reported in the literature. When the bladder itself is involved, it is his custom to put a two-way Foley catheter into the bladder and carry on continuous irrigation with Solution G until the urine becomes clear of incrustations and crystals. In some cases this is accomplished in three or four days; in others, a week or ten days of constant irrigation is necessary.

Internal medication with mandelic acid, ammonium chloride, or any of the mandelic products may be necessary adjuncts to the therapy.

This perhaps is one of the most progressive steps in the future treatment of phosphatic calculi and as an aid in the prevention of phosphatic calculi following surgical attack upon the urinary tract.

### BICHLORIDE OF MERCURY POISONING

A case of bichloride of mercury poisoning is reported where the patient was admitted to the hospital 48 hours after taking an unknown quantity of bichloride of mercury tablets. The individual was suffering from persistent diarrhea, nausea, anorexia, weakness, abdominal cramps, restlessness, nervousness, and inability to sleep. He had chills and fe-

ver, and was in total anuria for 24 hours prior to admission. This total anuria continued for three days. The left kidney was decapsulated on the third day. At that time the blood urea nitrogen was 105 mg. per 100 cc. Venesection-blood transfusions and parenteral fluids were begun immediately thereafter. For 14 postoperative days, he received a total of 23 venesection-transfusions. On the fifth hospital day the patient voided 35 cc. of urine and the urinary output increased progressively from that time on.

A constant check was kept upon the daily output of urine from the right non-decapsulated kidney and the left decapsulated kidney, and four weeks later the function of the decapsulated organ was definitely the better. Six weeks later, the same condition prevailed, the left decapsulated kidney apparently putting out the greater quantity of both fluids and solids.

At the time of discharge, two months later, the blood pressure was 115/78. The blood urea nitrogen was 14 mg. per 100 cc., creatinine 1.5 per 100 cc., and carbon dioxide combining power 6.1.

The method of combating acidosis is routine. It consists of giving alkalis orally, usually in the form of *sodium bicarbonate*. If there is vomiting, the sodium bicarbonate can be administered by *Levine* or *Miller-Abbott tube*. An alkaline-ash diet is given if the patient is able to take nourishment. Alkalis may be given intravenously in the form of 5 per cent solution of sodium bicarbonate, 500 cc. every 24 hours and at times as much as 50 Gm. of sodium bicarbonate is given in this manner in a 24-hour period. The carbon dioxide combining power level of the blood is the index guidance as to the amount of bicarbonate to be administered. *Aminophylline*, 20 cc., alternated with *magnesium sulfate*, 10 cc. of a 10 per cent solution intrave-

nously, is given two to three times during a 24-hour period to assist diuresis.

Water balance is observed by watching the edema of the lower extremities, the tenseness of the calves of the legs, the abdomen for evidence of fluid, the chest for pulmonary edema and possible effusion into the pleural and pericardial sacs. Should fluid retention appear, solutions are interrupted or decreased to minimal amounts of hypertonic glucose.

Multiple transfusions and venesections are considered a contributory factor in temporary detoxification of the blood and to prevent uremia during that period when little or no nitrogenous waste material is excreted and also to replace depleted blood proteins.

One case as carefully studied as this one is very important. It is the opinion of many men who have had considerable experience with decapsulation that the operation is not usually justifiable in cases of this kind. The great mass of evidence in the literature is against decapsulation. It is of course difficult to evaluate even in such a carefully studied case as this whether decapsulation really had as large a part in this patient's recovery as did the other methods of treatment, all of which are definitely indicated and rationally used.<sup>21</sup>

## THE PROSTATE

### Carcinoma

The treatment of carcinoma of the prostate has made great strides during the past few years. The fact that chemical substances are created in the testes which have definite action upon the epithelium of the prostate is now beyond dispute. Hormones undoubtedly play their part in simple hypertrophy but acid phosphatase plays an important rôle, not only in the causation of prostatic cancer but in the diagnosis and treatment of the

disease. The type of prostatic cancer that is amenable to deficiency therapy is the adenocarcinoma. Given a case of adenocarcinoma of the gland, with or without metastasis, the treatment is to destroy the interstitial cells of the testes. This, according to some observers, can be done by radiation of the testes. According to other observers, x-ray therapy cannot be given in sufficiently safe dosage to accomplish this result.

Other men believe that the exhibition of the female hormones in large enough dosage and over a sufficiently long period of time will so neutralize the male hormones that the prostatic cancer will stop growing and actually recede. That some definite improvement in these cases has been obtained cannot be denied; however, it is the belief of the majority of workers that adenocarcinoma, with or without metastasis, can be best controlled, perhaps actually cured by *surgical removal of the spermatogenic tissue* of the testes.

However, it is worthy of note that adult prostatic epithelium, whether normal, hyperplastic, or malignant, will undergo regression and atrophy when the androgens are reduced in amount, either by castration or by inactivation by the use of estrogens such as *diethylstilbestrol*. Many workers have reported these regressive changes in both ordinary hyperplasia as well as prostatic malignancy. It has been definitely demonstrated that if, even after orchiectomy, *androgen testosterone dipropionate* is injected, pain will recur and the serum acid phosphatase levels will rise, while it has been definitely proven that even after orchiectomy it is necessary to treat a large number of these cases of prostatic cancer, both with and without metastasis, with some form of stilbestrol. This is particularly indicated in those patients

who develop hot flashes and temporary edema of the ankles.

Clarke and Viets<sup>22</sup> report one interesting case where there was almost complete blockage of the cerebrospinal fluid in the lumbar spine below the twelfth thoracic vertebra and the fifth lumbar vertebra as a result of metastatic prostatic carcinoma.

This patient was admitted to the Neurological Service of the Massachusetts General Hospital because of extreme difficulty in walking and severe pain in his legs. The pain was intensified by walking, coughing, or straining. There were no symptoms of prostatic obstruction, although x-ray examination revealed a definite carcinoma of the prostate with osteoplastic metastases involving the first three lumbar vertebrae. The severe pain and other symptoms were due to the blocking of the cerebrospinal fluid from pressure or traction on the spinal nerve routes.

The patient was treated with diethylstilbestrol, 10 mg. intramuscularly, daily, and the patient felt better in 12 hours, was walking without pain in four days, and regarded himself as well eight days after treatment. He was discharged from the hospital on the thirteenth day of treatment with orders to take diethylstilbestrol, 6 mg. daily by mouth. Three weeks after discharge, because of certain sex characteristics which had developed, the dosage was reduced to 3 mg. a day by mouth. Seventy-seven days after treatment was started, he was re-admitted to the hospital for study, having received a total of 120 mg. of diethylstilbestrol intramuscularly and 231 mg. orally. The result was almost miraculous. However, three months later his symptoms returned and bilateral orchiectomy was done. The orchiectomy seems to have cleared up his symptoms quicker than the treatment with diethylstilbestrol.

Dean, *et al.*<sup>23</sup> state: "In our limited experience the clinical benefit which follows the oral administration of stilbestrol is as great as that which follows surgical castration."

Haines<sup>24</sup> concludes:

1. Sixty-six and two-thirds per cent of our prostatic malignancies were benefited by castration and/or estrogenic therapy.

2. Insufficient criteria have been developed to prognosticate which are the cases that will respond to castration and estrogenic therapy. (The metastatic ones seem to do best.)

3. Perineal biopsy is to be preferred to resection biopsy. The latter may miss the carcinomatous area.

4. The question of optimum dosage is yet to be settled.

5. Some studies should be directed to the action of estrogen on water balance and blood electrolytes.

6. Some studies should be directed to the action of estrogen on other endocrines (*e. g.*, thyroid, adrenal, and pituitary).

7. Estrogenic action seems to be inhibited by infection.

8. Estrogens relieve the symptoms of prostatism in many cases and also cause regression in size of the prostate.

9. Estrogens help relieve the common symptoms of bladder malignancy (in males).

10. Estrogens seem to cause both clinical and cystoscopic improvement in mild (Grade 1) carcinoma.

11. Estrogenic value in bladder malignancy in females is questionable.

12. Bladder malignancy may cause an increase in acid phosphatase.

Huggins<sup>25</sup> says: "The question of inactivation of androgens by estrogens in prostatic cancer as opposed to castration naturally arises. The type of endocrine castration as opposed to surgical castration is at first glance attractive since it can be carried out without surgery and is financially economical. However, it is unsound, since the inhibition of the androgens by estrogen is not complete and a complete inhibition or elimination of androgens is the basis for the modern treatment of advanced prostatic cancer;

moreover, this partial inhibition is temporary and estrogen must be administered for a long period of time. Further, in many species the administration of estrogen to males for a long time is in itself a carcinogenic. While it was first shown in this laboratory that beneficial results occur in prostatic cancer from both surgical castration or estrogen administration, we feel that bilateral orchiectomy is the method of choice as a basic treatment in advanced or metastatic prostatic cancer."

The use of sterilized pellets of diethylstilbestrol implanted subcutaneously has more advantages over the injection treatment and the administration of the drug by mouth. These subcutaneous implantations are made through a paracentetic trocar, after a small incision has been made through the skin in the seventh intercostal space at the posterior axillary line. The pellets are implanted at least 2 cm. away from the incision. The skin incision is then approximated with sterile tape and usually heals within 48 hours. After the first 50 days from 40 to 60 per cent of the weight of the pellets are absorbed and it takes 100 days for from 70 to 90 per cent of the original weight to be absorbed. Therefore, one 50 mg. pellet delivers an average of 0.5 mg. per day for 50 days and an average of 0.4 mg. per day during a 100-day period. From five to eight weeks after the pellets are implanted, there is enlargement of the breast. However, there have been no toxic reactions and where the drug has been used in this manner on neoplastic disease, the observations have been insufficient to evaluate the effects of the therapy. However, in some of the patients there was relief from pain within two weeks and an elevated serum acid phosphatase approximated the normal line. It is doubtful if this therapy will take the place of the administration of

the drug by mouth or by hypodermic injection, and it will have little effect other than being palliative in the inoperable prostatic carcinoma.<sup>26</sup>

### Treatment of Acute and Chronic Prostatitis

In general, the treatment of acute and chronic postatitis is by *heat* and *protection from trauma*, and that of subacute and chronic prostatitis by *prostatic massage*. The *sulfonamides* may be helpful. Acute prostatitis, whatever the cause, is best treated by complete bed rest for all febrile cases and the avoidance of foods which irritate the urinary tract. Sexual excitation should be avoided and all local treatment, such as urethral or bladder irrigations and rectal manipulation, should be discontinued. Heat is beneficial and may be obtained by *hot sitz baths*, by the application of heat directly to the prostate, by *rectal irrigations* or *diathermy*. The bowels must be kept well open to avoid pressure of a hard stool against the prostate. If prostatic abscess is suspected, only the most gentle palpation should be done to diagnose it.

**Sulfathiazole**, 1 Gm. (15 gr.) every four hours, together with sufficient alkalis, such as sodium bicarbonate, should be exhibited for not more than ten days. Following the subsidence of the acute symptoms, local treatment may be instituted.

**Chronic Prostatitis**—Here the principal thought is to establish adequate drainage of the infected prostatic ducts. This may be easy or difficult to attain. However, once the diagnosis is established, massage of the prostate by rectum is the most important single measure. Some men massage the prostate as often as twice a week, prolonging the in-

terval between the massages as the amount of pus diminishes. Massage increases the blood supply, helps to evacuate pus, bacteria, and debris from the prostatic ducts and should never be done vigorously. Usually the prostate should be massaged on a full bladder, the patient voiding immediately thereafter. A search should always be made in chronic prostatitis for a urethral stricture and, if found, it should be treated, and even when such a condition cannot be found, overdilatation of the urethra will serve to permit better drainage from the prostatic ducts. Again, this treatment should not be overdone.

The treatment of chronic prostatitis by *intraprostatic injections* of various antiseptic solutions has few advocates.

If there is a great deal of fibrosis in the prostate, any blood-borne medication, such as the sulfonamides, will prove of little benefit. Their use might, however, help to prevent an epididymitis.

If the patient's chronic prostatitis does not respond to the treatment as outlined, then urethroscopic examination is essential and necessary.

It must be kept in mind that the prostate can be infected from distant foci of infection and that the organ may not respond to therapy until the original focus is removed. If the prostate is chronically infected from an upper respiratory or intestinal infection, the removal of the primary focus may not be sufficient to cure the chronic prostatitis and, if left untreated, it will then become a primary focus of infection.

The prognosis in the vast majority of cases is good and even in those with sexual dysfunction, while the prognosis is difficult to evaluate, the probability is that the patient will be very much improved by intelligent treatment.

## CHANCROIDAL DISEASE

Chancroidal disease is caused by the bacillus of Ducrey, and in an experimental study with 28 inoculations in 170 areas on 19 volunteers recently, the disease developed in 30 controlled inoculations. The application of castile soap and water, surgical soap solution, calomel ointment, silver picrate jelly, or a mercurial antiseptic, proved to be a useless prophylactic in every instance.

**Sulfathiazole** administered orally following inoculation, before inoculation, as well as before and after inoculation, prevented the production of an experimental chancroid. Oral administration, however, if used from three to five days after exposure, did not prevent the disease. Antibacterial agents in the form of sterile powders, such as **sulfathiazole**, **sulfanilamide**, **sulfadiazine**, and **succinylsulfathiazole** sprinkled over the inoculated areas proved effective. **Tyrothricin** similarly used was of no value. **Five per cent sulfathiazole in water** proved useful in five of 12 inoculations. Other combinations, such as 5 per cent sulfathiazole or sulfanilamide, 2 per cent urea, and 26 per cent cod-liver oil, were not as efficacious. Twenty-five per cent sulfonamide in water was only partially successful.

A mixture containing at least from **20 to 25 per cent sulfonamide**, made by the addition of sulfathiazole or one of the sulfonamides to **calomel ointment**, proved promising as an effective prophylactic. A mixture containing from 20 to 33 per cent sulfonamide and from 25 to 33 per cent calomel proved successful in preventing the disease. Since the incorporation of a sulfonamide in the calomel prophylactic tube now generally used, it gives us a prophylactic against chancroid and it is hoped that it will not minimize the effectiveness of calomel in the prevention of syphilis.<sup>28</sup>

## URETER

A new operation for ureteropelvic stricture, plastic operations upon the pelvis of the kidney, and even upon the kidney itself have added a great deal to the knowledge of the anatomicopathological conditions that exist in the upper urinary tract, and a stimulation to conserve renal parenchyma has resulted from the study of surgical attacks upon conditions in the upper ureter and the pelvis of the kidney. This has brought forth a large number of papers concerning the surgical treatment of lesions of the upper ureter and pelvis.

There are many obstructions that have been treated conservatively by various methods to the total satisfaction of the operator and which will result in the saving of a large number of kidneys that otherwise would have been sacrificed. However, it has been proven that those cases of plastic repair have done poorly unless the ureter has been splinted for various periods of time. With this information at hand, Davis<sup>29</sup> has found it possible to devise an operation for strictures of the ureter that has worked extremely well. Many a kidney may be saved regardless of the type of ureteral obstruction by this technic.

In the **intubated ureterotomy** no effort is made to draw the tissues into a new form by the use of sutures. As a matter of fact, no sutures at all are used. The operation depends upon the physiological repair processes of the tissues. The splint is a mold upon which the tissues, by their own proliferation, re-form the ureteral channel in normal size and shape, and it must be left in place until this proliferation is completed, and the new channel lined by epithelium; thus a new, normal sized channel replaces the old strictured one.

In the use of a ureteral or ureteropelvic splint, the size of the splint, its shape,

and the length of time it is left in place are the most important points. Many of the splinting tubes have been too small. The tubes should be large enough to enter the uncut or normal portion of the ureter without fitting so tightly as to cause ischemia, nor must the splint be withdrawn too soon. The allowance of time for the tissues to reconstruct themselves should be generous and the splint

should be left in a long period of time. Three weeks may be enough; however, it has been the experience of many urological surgeons that a splinting catheter should not be taken out under five weeks and some go as far as to say that such a splinting catheter should be left in a minimum of six weeks.

Operative technic is well illustrated by the accompanying drawings.

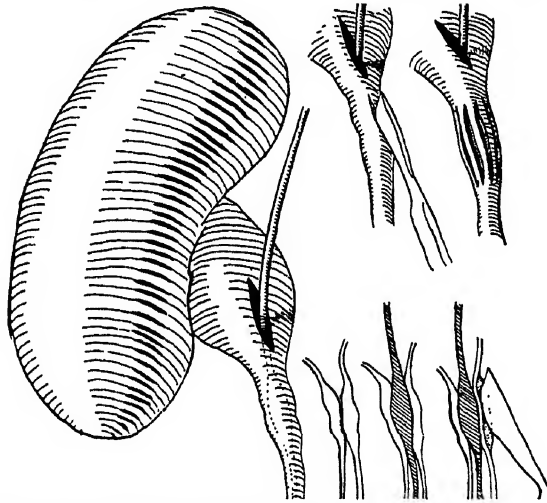


Fig. 1.—Rammstedt type operation for thick-walled ureteral stricture. The stricture is stretched by a bougie inserted through a pyelotomy incision; one or more longitudinal incisions are made passing through all layers of the ureteral wall except the mucosa. (D. M. Davis: Surg., Gynec. and Obst.)

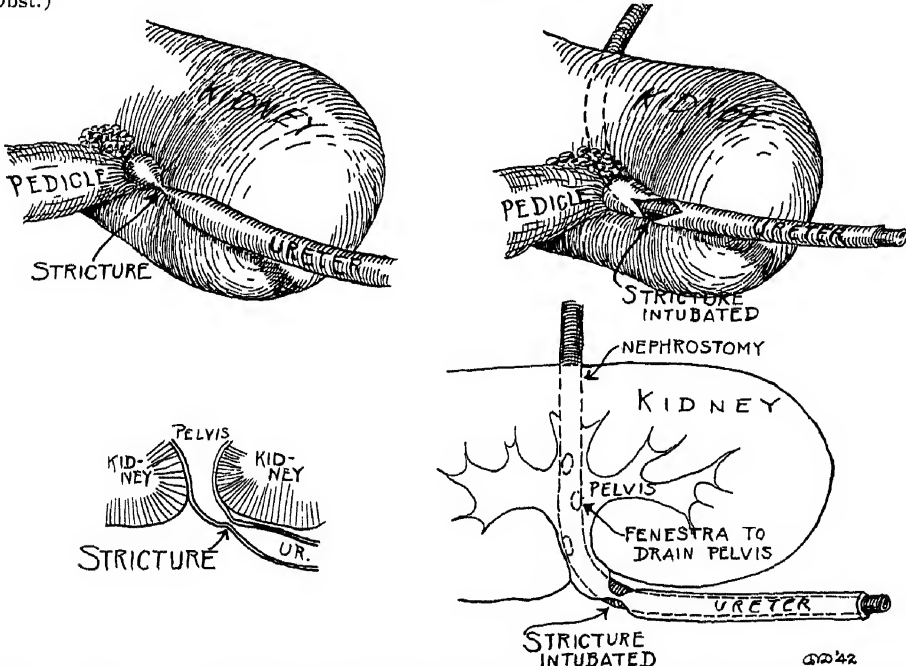


Fig. 2.—Case 1. a, Conditions as found at operation; b, diagrammatic section through ureter as it entered kidney; c, stricture incised, splint tube in place in ureter, proximal end brought out through nephrotomy incision; d, diagrammatic section showing conditions at end of operation. (D. M. Davis: Surg., Gynec. and Obst.)



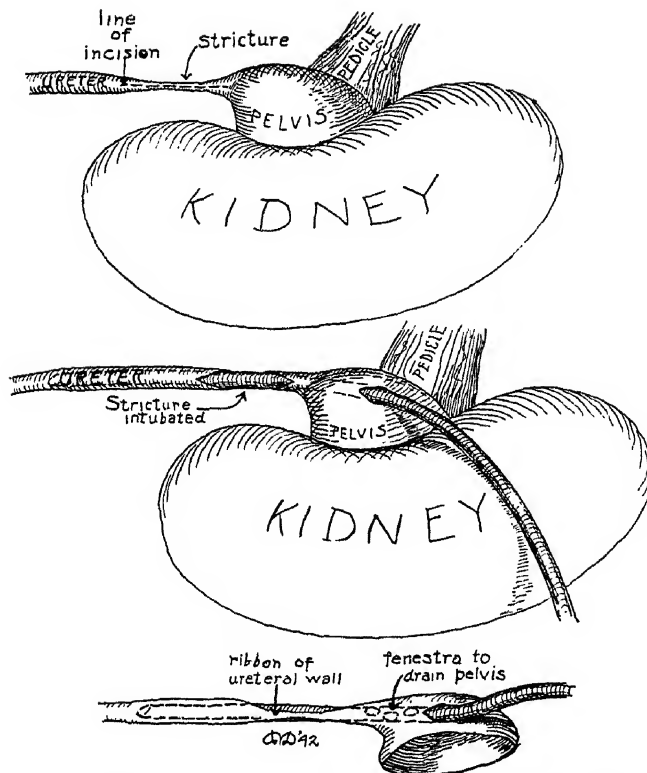


Fig. 3.—Case 3. a, Conditions as found at operation. The stricture is actually a little below the ureteropelvic junction; b, stricture incised, splint tube in place, proximal end brought out through pyelotomy incision; c, diagrammatic representation of conditions at end of operation. (D. M. Davis, Surg., Gynec. and Obst.)

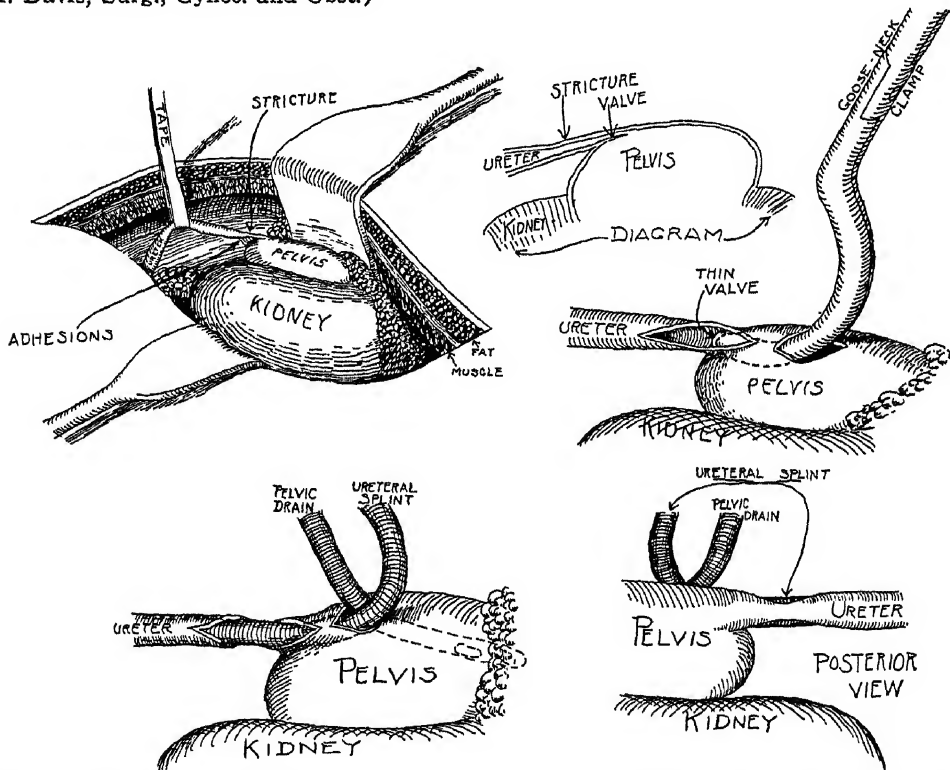


Fig. 4.—Case 4. a, Conditions as found at operation; b, diagrammatic section of ureter and pelvis, showing stricture and valve; c, valve pushed down into ureter by tip of clamp; d, stricture incised, valve removed, splint tube in place, with proximal end brought out through pyelotomy incision, separate drainage tube in pelvis; e, posterior view at end of operation, showing ribbon of ureteral wall along splint tube. (D. M. Davis: Surg., Gynec. and Obst.)

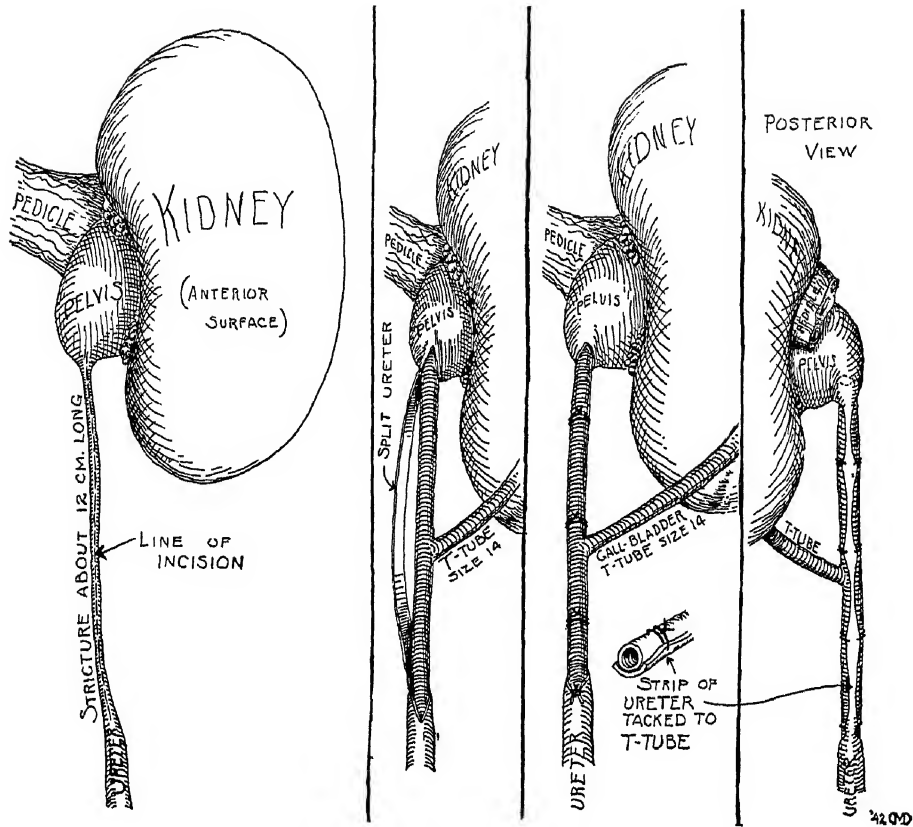


Fig. 5.—Case 7. a, Conditions as found at operation; b, stricture incised through its entire length, T-tube in place. Note that ureteral ribbon does not stay in contact with tube; c, ureteral ribbon held to T-tube by sutures; d, posterior view, showing ureteral ribbon closely applied to T-tube. Stem of T-tube provides urinary drainage. (D. M. Davis: Surg., Gynec. and Obst.)

### Carcinoma of the Ureter

Primary carcinoma of the ureter is far more prevalent than has heretofore been believed. The diagnosis is usually made by cystoscopy and careful ureterograms. There have been more than 180 cases reported in the literature.

The vast majority of these growths are papillomatous in the beginning and are relatively benign if diagnosed early and do respond to radical surgery. If, after a careful study of a given case, there is a suspicion that tumor exists in a ureter, surgical intervention should not be delayed. The approach should be extraperitoneal. If the presence of ureteral tumor is revealed, a complete *nephro-uretero-partial cystectomy* should be done at once. It is necessary to take out a portion of the bladder wall because in

52 per cent of the cases reported the tumor was in the lower end of the ureter. If a diagnosis of tumor can be made positively, prior to operation, the treatment of the lesion by *radium catheters* and *x-ray therapy* prior to surgical attack may be considered good therapy. However, no consideration of either x-ray or radiation therapy should be permitted to be a substitute for radical surgery.<sup>30</sup>

### URETHRAL CARUNCLE

Urethral caruncle is a very common lesion in women. The symptoms are usually those of frequency and urgency of urination, burning, and bleeding, combined with a decided reflex mental attitude because of the sensitivity when this irregular granular mass is touched. The

increase in the mental apprehension becomes greater if the patient has been able to observe the lesion. There is the external caruncle which is easily seen and the intraurethral caruncle which is the more frequent and produces symptoms as a result of obstruction. The differential diagnosis between the benign caruncle and primary carcinoma of the urethra is important. The intraurethral type is usually located behind a tight or constricted meatus and may be so small that it is easily overlooked. However, if the urethra is carefully anesthetized, it may be made to protrude from the meatus. A search should be made for other pathological conditions.

All of these cases are surgical and must be treated by either *fulguration* or *surgical removal*; however, if fulguration is used, a sufficiently large piece of the bleeding inflammatory mass should be removed for pathological diagnosis.<sup>31</sup>

Careful pathological study of caruncles has seemed to prove that they develop from the ectropion of the posterior urethral wall and are caused by postmenopausal shrinkage of the vaginal tissue; that the further changes of the everted mucosa are secondary and caused by the altered environmental conditions, and that the condition is not the result of inflammation of the urethra or bladder and is therefore entirely secondary. It is believed that simple removal or cauterization of the caruncle is not sufficient but that the entire everted mucosa should be carefully excised and that the wound should be carefully sutured.<sup>32</sup>

Many of these so-called benign caruncles may be either carcinomatous or precancerous, and while it is admitted that carcinoma of the female urethra is infrequent, it must be remembered that any dependence upon the symptomatology and the clinical appearance of the tissue carries grave risks, and where malignancy

is advanced to the point where clinical diagnosis is possible, the patient's condition is usually hopeless. All of the removed tissue should be carefully studied pathologically.

Treatment must be based on two considerations: First, the growth must be completely removed or destroyed, and, second, sufficient mucous membrane of the base must be removed to prevent recurrence. Because of its distortion of the field, local anesthesia should be eliminated and a general anesthetic, such as *intravenous pentothal sodium* should be used. After the urethra is overdilated the caruncle or tumor should be completely removed by an electric cutting loop, while bleeding of the base is controlled with the coagulation current. Early malignant growths have been just as effectively cured by this method as has been the early caruncle. However, if there has been any extension beyond the immediate local area, further surgery of a more radical nature must be considered.<sup>33</sup>

**Meatotomy:** Adequate diagnosis and treatment of urethral disorders is not feasible when a small meatus is present. A small meatus is one that will not admit a 26 F. bulb. In these cases meatotomy is necessary for diagnosis, as well as treatment, particularly where the conditions to be treated are chronic, such as recurrent urethritis, deep urethral irritation, and strictures. Incision of a small meatus is accomplished, usually after the injection of 1 per cent solution of *procaine hydrochloride* into the tissue between the meatus and the frenum. After such a meatus is incised, the urethra should be tested for strictures by introduction of bulbs. A sound one size smaller than the largest bulbous bougie which would pass through the anterior urethra is then introduced through the deep urethra. After the sound is re-

moved, the incised area at the meatus is swabbed with *Monseil's solution*. This stops bleeding and lessens the discomfort when voiding. The patient is then instructed to introduce a glass rod, such as is attached to the stopper of germicidal solutions, about three-quarters of an inch into the urethra and to press downward after voiding to prevent the cut surfaces from growing together. If this procedure is carried out nightly for ten days, the mucosa will have covered the incised surface and leave a large meatal opening.

Urethral strictures, either acquired or congenital, or both, require treatment. The recognition of a narrowing point in the urethra is easy and is very important, and includes the introduction of bulbous bougies into the anterior urethra to ascertain where these constrictions are, provided, of course, the channel is not acutely or subacutely inflamed. Sounds are of no value in the diagnosis of urethral strictures because large calibered strictures through which a sound passes easily may be associated with and the cause of chronic discharges which will not clear up until after the stricture is treated. These same strictures may be the cause of low backache and postpubic or pelvic discomfort, while itching along the urethra or in the perineum is one of the commonest signs of urethral stricture. Frequency of urination, nervousness, and sexual disturbances are also common symptoms. It is interesting to note that strictures of large caliber may be attendant with more symptoms than fairly tight ones. Retention of urine, partial or complete, after exposure to cold, sexual excess, alcoholic excess, or voluntary retention may result from strictures of fairly large caliber.

Following transurethral resections of the prostate, previously existing strictures may cause a great deal of trouble

and will require dilatation. Treatment by gradual dilatation is the method of choice in the management of these lesions and the dilatation should be so gradual that the trauma should not be sufficient to require repair by further scar tissue. Anesthesin jelly injected into the urethra and held in for about five minutes will permit the passage of instruments without any great discomfort to the patient. If difficulty is found in passing small sounds, filiforms should always be used followed with bougies of such size as to not create further trauma. Suprapubic drainage of the bladder is sometimes necessary when false passages, periurethral abscesses, or fistulas are present.

In the deep urethra the symptoms are painful and if the prostate is involved, the *sulfonamide drugs*, *hot baths*, and *palliative measures* are required. Failure to recognize disorders of the prostatic urethra is due largely to failure to suspect them as being associated with the more or less ill-defined symptoms produced.

Hyperemia and hyperesthesia of the deep urethra respond so well to treatment with sounds and instillations of one or two per cent solution of *silver nitrate* that more elaborate diagnostic measures than this response to treatment are not required.

The most common condition caused by abnormalities of the verumontanum is the so-called sexual neurosis which is associated with mental disturbances or nervousness all out of proportion to the pathological process involved.

Unfortunately disorders in the prostatic urethra are not characterized by lesions always discernible by cystourethroscopic study. They are made just as obvious by appropriate remedial measures. The cure of these conditions is very convincing. Not that adequate study should not be made, but not infrequently

appropriate treatment with sounds and medication to the prostatic urethra will correct symptoms not assignable to any lesions sufficiently gross to recognize endoscopically.

Appropriate treatment of hyperemia and hyperesthesia of the verumontanum consists in correcting certain etiologic factors such as prolonged necking without sexual gratification, masturbation, withdrawal before emission, and other such abnormal habits. Full sized sounds introduced into the bladder and permitted to remain in the urethra for approximately ten minutes should be done once a week. These tend to lessen the deep urethral hyperesthesia and hyperemia and are found to be of value even though strictures are not present. After tolerance to these treatments has been acquired and if symptoms still persist, a cystourethroscopic examination should be made.

**Backache**—It is remarkable how low backache in the male will respond to urethral dilatation plus massage of the prostate gland. It is impossible to know why this relief is obtained. In the event of unidentified low backache, even though the prostate shows few or no pus cells and no strictures are detectable, the treatment will relieve a large percentage of these patients.

**Enuresis**—If bed wetting is not caused by some definite condition, it will be controlled in from one to ten treatments if a meatotomy is done. This works in both sexes. The urethra is then dilated once a week. Occasionally, in boys it is necessary to instill one or two per cent solutions of *silver nitrate* into the deep urethra after each treatment with a sound. Many cases of intractable enuresis have been cured by this method of procedure, even though no pathological lesions could be found to account for the difficulty.<sup>34</sup>

## UROGRAPHY

The estimation of renal activity, both from an anatomical and physiological point of view, can be fairly well determined by excretory urography. Most of the information obtained from urographic studies has been anatomicopathological. As regards urinary tract function, urography may be of value in estimation clearance by the roentgen appearance of the dye and by studying the appearance of the dye in the urinary tract. If kidney function is normal, dye clearance as determined by urography can be fairly accurately estimated. It has been determined that the rate of iodine excretion is roughly proportional to variations in urea clearance.

Jarre and Cumming, using their Cinex-camera roentgenography, have contributed a great deal to the knowledge of kidney physiology, demonstrating movements of the renal pelvis, while multiple exposures and films made in various positions can also give information of a similar nature. Anything which disturbs the transportation of the urine to the bladder can be observed and the clearance of the contrast medium and the whole excretory mechanism of the kidney can be studied and estimated. Intrinsic lesions of the bladder, as well as lesions of the adjacent and spinal cord structures, may not only produce but secondarily cause dysfunction of the upper urinary tract, and the study of the ability of the bladder to empty itself during urography may give a clue to a diagnosis.<sup>35</sup>

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## VENEREAL DISEASES

PAUL R. LEBERMAN (MC), U.S.N.R.\*

In reviewing this year's literature on venereal disease, one must keep in mind its importance in its effect on our war effort. In the last war, over seven million man days were expended. Today, with our armed forces so tremendously increased, as well as our civilian communities taxed to capacity by transients from all parts of the country, our venereal disease incidence and problems present greater difficulties than one could ever cope with.

Specially noteworthy in this year's literature is the discovery of *penicillin*, which is so effective in producing a cure in gonorrhea; with syphilis one must be cautious—the results in a few cases are promising—time will tell.

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\* The opinions and assertions contained herein are those of the author and are not to be construed as those of the Navy or of the Naval Service at large.

Contributions from foreign countries are of necessity sparse. It becomes evident that we must rely more on American contributions, and they compare well if not better than those of other countries in substance and in scientific achievement.

The proper treatment of gonorrhea by means of the *sulfa drugs* assumes an important problem in this year's literature. The Public Health Services continue their activities in clinical, social, and scientific attacks on gonorrhea, syphilis, and other venereal diseases.

Reports from various clinics on results obtained in a large series of cases treated with *sulfonamides* are very ably discussed. Continued use of *fever therapy* in the treatment of gonorrhea definitely establishes it as a useful addition to our treatment armamentarium.

Pappas,<sup>1</sup> in the *Military Surgeon*, discusses the venereal disease problem in the U. S. Army. Between April 1, 1917, and December 31, 1919, the mean strength of the U. S. Army was 4,182,479 men. Primary admissions of venereal patients were 86.6/1000, 10.2 per cent of total "sick" admissions of the Army, and in excess of the killed and wounded by approximately 10,000 cases. The history of venereal disease in the U. S. Army from 1918 to date is reviewed and the various methods of control discussed. Present-day methods of control consist mainly of education of officers and men, morale-building activities, prophylactic measures, adequate treatment of infected men, and disciplinary action with forfeiture of pay for venereal disease cases. Control of venereal disease in the population adjacent to military camps is a civilian problem but has the coöperation of the Army. Rigorous repression, rather than segregation, of prostitution is the essential method of control. The author assumes the sex act to be a psychologic rather than a physiologic urge and believes that measures to attune the mind, decrease temptation, and lessen opportunities, will prove effective.

Carter,<sup>2</sup> as National Advisory Police Commissioner on Social Protection, in a statement on venereal disease in the U. S. Navy, reports that the incidence of all venereal diseases in the U. S. Navy was 80, 51, and about 36/1000 in 1940, 1941, and 1942, respectively. Ten leading cities in 1942 were the source of 41 per cent of all cases in the Navy for which data were available, and of 57 per cent of the (Navy) venereal disease cases originating in the U. S., foreign ports caused only 28 per cent of the Navy venereal disease cases in 1942.

The presence of *Neisseria gonorrhoeae* cannot be proved by the presence of gram-negative diplococci in a smear.

De Bord<sup>3</sup> reports that the examination of reports of the smears of 147 individuals with conjunctivitis, vaginitis, or normal vaginas revealed 45 instances of *Mimae*, 6 of gram-positive diplococci tending to lose the stain, and 8 of *Neisseriae*. The organisms isolated were *N. gonorrhoeae*, *N. flava liquefaciens tarda*, *N. catarrhalis*, *N. intracellularis*, and *N. gigantea*, *Mima polymorpha*, *M. polymorpha* var. *oxidans*, *Colloides anoxydana*, *Herellea vaginicola*, and the gram-positive diplococci which lose their stain. Approximately 40 per cent of the organisms seen in a smear are wrongly called gonococci; cultural methods must be used for correct identification.

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## GONORRHEA

Ruth B. Thomas<sup>4</sup> reviews the literature from January, 1938, to January, 1942, on the gonococcus and infections caused by it. She suggests that sulfonamides and gonorrhea prophylaxis after exposure should be investigated.

M. R. Soni,<sup>5</sup> in the *British Medical Journal*, states that a four-day cure of gonorrhea with *sulfathiazole* can be expected if treatment is started just as the inflammation is beginning to show itself in the mouth of the urethra (about four days after exposure), but not if treatment is delayed (as is usually the case) until the discharge is fully established. For successful treatment, all patients, especially soldiers, should be put on sick list for two weeks, ordered to irrigate with 1:4000 permanganate three times a day by a bulbous-end glass syringe, and given *sodium sulfathiazole*, 1 Gm. (15 gr.) every four hours for robust patients, every six hours for non-robust patients, day and night for four days. It is important to free the patients not only of gonococci but of other organisms. The great increase in nonspecific



vaginitis in young women may be due to incomplete therapy of male gonorrhea patients.

K. R. Ogilvie,<sup>6</sup> in the same journal, recommends local treatment of gonorrhea by efficient *urethral irrigation* for four to five days before giving a *sulfonamide*. Approximately 100 cases have been seen of chronic urethritis allegedly due to inadequate chemotherapy or to what is considered adequate chemotherapy given without any local treatment.

James P. Pappas<sup>7</sup> states that of 72 soldiers with acute gonorrhea treated by *sulfadiazine*, 88 per cent became "dry" in an average of 4.7 days, showed negative smears in an average of 2.4 days, and gave clear 2-glass urine tests in an average of 2.6 days, although shreds persisted in the first glass for a variable period afterward. The remaining patients either failed to respond or relapsed. Average hospitalization period was 11 days. Dosage was 6 Gm. (90 gr.) daily for 2 days, then 3 Gm. (45 gr.) daily for 8 days, supplemented by 1.5 Gm. (22.5 gr.) *NaHCO<sub>3</sub>* to inhibit sulfadiazine crystals in the urinary tract, and also supplemented by adequate and early drainage of glandular structures communicating with the urethra, if indicated. Toxic reactions comprised one moderate febrile reaction and one instance of dermatitis with fever. Among 65 and 55 soldiers treated for fresh gonorrhea with *sulfapyridine* and *sulfathiazole*, respectively, 85 and 89 per cent were cured, as compared with the 88 per cent cure rate in the sulfadiazine group. Toxic reaction rates with sulfadiazine, sulfathiazole, and sulfapyridine were 2.6, 3.0, and 5.4 per cent. From these results and others which are reviewed, Pappas concludes that in gonorrhea sulfadiazine is at least as effective and as well tolerated as sulfathiazole, and is useful both as an additional primary

drug for that disease and as a valuable secondary drug for infections which have not responded to sulfathiazole originally.

It is reported by the New York City Health Department<sup>8</sup> that *sulfathiazole* should be accepted as a drug for the treatment of all gonococcal infections. They recommend a 5- and a 10-day plan of therapy. The 5-day plan, preferred unless there are indications for the longer course, consists of 1 Gm. (15 gr.) sulfathiazole 4 times a day, after each meal and at bedtime, for 5 days. Dosage in the 10-day plan is 0.5 Gm. (7.5 gr.) every 4 hours for 4 doses a day. It is unnecessary to give local treatment or to conduct routine examinations of blood and urine. Serious toxic reactions, requiring stoppage of treatment, rarely occur. Mild toxic reactions, which rarely require stoppage of treatment, include slight gastrointestinal disturbances and dizziness. Marked clinical and bacteriological improvement ordinarily occurs in 48 to 96 hours, but the full planned course of treatment should nevertheless be continued. If the patient is not cured by one course, the course may be repeated after a rest period of one week, during which mild antiseptics are given. Hospitalization is usually unnecessary. Acute gonococcal salpingitis requires *rest in bed*; the suggested oral treatment is *sulfathiazole*, 2 Gm. (30 gr.) per day. Pelvic or Bartholin gland abscesses always need *surgery*. All patients should be given routine serologic examinations for syphilis.

Jefferies and McElligott,<sup>9</sup> in the *Lancet*, report a series of 567 patients with gonorrhea at a Royal Air Force hospital treated by *sulfathiazole* in varying dosages, the optimal dosage from points of view of economy and of efficacy being 6 Gm. (90 gr.) daily for 2 days. Among 143 cases treated with 6 or 8

Gm. (90 or 120 gr.) on the first day and 6 Gm. (90 gr.) on the second, 89.5 per cent were cured. Somewhat less satisfactory results (82.2 per cent cures) were obtained with 4-, 8-, and 12-hour courses of 10, 10 and 8 Gm. (150, 150, and 120 gr.) sulfathiazole in 129 cases. Drug rash appeared in a few cases given further chemotherapy after a first course had failed. Transient toxic symptoms of sulfathiazole were slight headache, nausea, and sensation of heat. Advantages of sulfathiazole over sulfapyridine for treatment of gonorrhea in the Services are lower toxicity and shorter duration of treatment.

John Petro<sup>10</sup> reports 956 patients having acute gonorrhea and treated with *sulfapyridine* or *sulfathiazole* in tablet form for 44 or 92 hours. A 16-Gm. (240-gr.) intensive 44-hour course comprised a first dose, 4 Gm. (60 gr.); a second, 2 Gm. (30 gr.); and subsequent 4-hour doses of 1 Gm. (15 gr.). In a 24-Gm. (360-gr.) course, 1 Gm. (15 gr.) was administered each 4 hours for 92 hours. With both methods the drug was given day and night. Subsequently, 12 Gm. (180 gr.), given in 1-Gm. (15-gr.) 4-hourly doses were prescribed for all patients who failed to respond satisfactorily to first course or who showed early clinical or bacteriological relapse. Urethral discharge usually subsided and gonococci disappeared within 24 to 48 hours. If discharge persisted, especially after a third course of treatment, resistance to the drug was diagnosed. Resistance to sulfonamide may be acquired, relative, or absolute. Five resistant and one relatively resistant strains of gonococci were responsible for failure of six cases to respond to sulfonamides. Host-to-host transmission of resistant gonococci strains is apparently possible. Too few treatments, too small dosage, or inadequate tests of cure probably ac-

count for apparently resistant strains in some instances. Sulfonamide resistant organisms must be treated by irrigations or artificial fever.

Leberman and Alexander<sup>11</sup> report the use of a new drug, *sulfathiazoline*, in the treatment of 88 male patients with gonorrheal urethritis. Seventy-seven passed all tests of cure after 1 Gm. (15 gr.) sulfathiazoline q.i.d. for ten days. Average duration of symptoms was 3.2 days. Blood levels varied from 0.6 to 4.0 mg. but seemed unrelated to curative action; their routine determination is not advocated. Toxic symptoms comprised only slight transient headache or gastric disturbance and did not necessitate withdrawal of the drug. Urethral stricture existed in all cases of anteroposterior infection not responding to the drug.

Frary,<sup>12</sup> in the discussion of present-day treatment in the male, states that upwards to 80 per cent of acute gonorrheal infections in the male can be cured with five daily oral doses of 4 Gm. (60 gr) *sulfathiazole* (two 0.5-Gm. [7.5-gr.] tablets after meals and at bedtime), or ten daily doses of 2 Gm. (30 gr.) *sulfadiazine* is equally effective; a second course may be given after five days if the first course was not curative; involvement of the posterior urethra does not respond to this treatment. A clear two-glass urine test is usually indication for anterior irrigation with a warm 1:8000 or 1:10,000 *potassium permanganate solution*. Extreme gentleness is essential in prostatic massage; if the posterior urethra becomes involved during treatment, all therapy should be stopped immediately and *hot sitz baths* and *bed rest* prescribed. When both first and second glasses of urine are clear, or nearly so, for two weeks, gentle massage of the prostate and tests of cure are indicated. Alcohol and sexual activ-

ity are prohibited. In some cases irrigation can be performed by the patient, using an asepto-type syringe and not more than 6 cc. of a 5 per cent weak or 0.5 per cent strong *protein silver solution* held in the urethra for five minutes. Excellent results have been obtained with this treatment by the Division of Venereal Disease Control, State Department of Health, Lincoln, Nebraska.

Osmond,<sup>13</sup> in a discussion of the modern treatments of gonorrhea in the male, states that accurate diagnosis and test of cure are based upon examination for gonococci of all-night urine, of expressed fluid following massage of prostate and seminal vesicles, examination of anterior urethra with urethroscope, introduction of a 22-26 Clutton curved sound into the bladder, and gonococcal complement-fixation test in therapy-resistant patients. If there is no history of intolerance to sulfa compounds, 5 Gm. (75 gr.) *sulfathiazole* a day, evenly spaced, for two to four days is prescribed with concurrent use of alkaline mixture and plenty of fluids. As a substitute, *sulfadiazine*, 6 Gm. (90 gr.) a day for four days. *Sulfapyridine*, or *sulfanilamide*, 5 Gm. (75 gr.) a day for five days, may be given. Sulfonamide therapy should be limited to seven consecutive days and a second course given only after a blood count. Irrigation, instruments, prostatic massage, or a syringe for intraurethral examination, etc., should be employed only by a specialist. Following one or two courses of chemotherapy, the patient should be examined once weekly for three weeks and finally at the end of three months. Gonorrhea in the female is treated similarly. Dry swabbing or swabbing with weak alkali may be done; douching is contraindicated. Microscopic, bacterial, and blood tests of cure should follow the menstrual

period for three consecutive months after termination of treatment.

Griswold,<sup>14</sup> in a comparative study of results of sulfonamides in the treatment of gonorrhea, reports 16 cases of gonorrhea given *sulfathiazole* and 15 given *sulfapyridine* in which the results were definitely superior with *sulfathiazole*.

In a rapid appraisal of sulfonamide drugs in the treatment of gonorrhea in the male, the American Neisserian Medical Society and U. S. Public Health Service<sup>15</sup> state that *sulfamerizine* is inferior to *sulfadiazine*, *sulfathiazole*, and *sulfapyridine*, but superior to *sulfanilamide*, in producing symptomatic and bacteriologic cures of gonorrhea in the male, according to a weekly progress chart. By the fourth week, the percentage of patients (total not given) who were both asymptomatic and bacterially negative was approximately 66, 83, 72, 70, and 30 for the drugs in the order named. Incidence of severe reactions was lowest (1.1 per cent) with *sulfamerizine* and *sulfathiazole*, 1.6 per cent with *sulfadiazine*, and 9.1 per cent with *sulfapyridine*.

Jacoby and Rosenthal<sup>16</sup> and Jacoby<sup>17</sup> state that of various sulfonamides (*sulfanilamide*, alone, with *vitamin C*, and with *gonococcus vaccine*; *Disulon*; *Aldanil*; *sulfathiazole*; and *sulfathiazoline*), *sulfathiazole* proved most effective in the cure of gonorrhea, chancroid, and lymphogranuloma venereum. A cure was considered to have been effected when six negative weekly cultures from the urethra and cervix had been obtained after cessation of medication. *Sulfathiazole*, 2 Gm. (30 gr.) a day for ten days, cured 89 of the 100 cases of gonorrhea. Fewer toxic reactions occurred when *vitamin C* was used with *sulfanilamide*; maximum incidence of reactions was 25 per cent in patients on *sulfanilamide* alone, 5 Gm. (80 gr.) for four days, or 2½ Gm. (40 gr.) for seven

days. The ten-day period of therapy had little advantage over the five-day period. In both plans, 20 Gm. (300 gr.) of either sulfathiazole or sulfathiazoline were divided into daily doses. Sulfathiazole, 2 Gm. (30 gr.) daily for 14 days, cured 90 per cent of cases of lymphogranuloma venereum. Sulfanilamide, 5 Gm. (80 gr.) in five days or  $2\frac{1}{2}$  Gm. (40 gr.) in nine days; sulfathiazole, 2 Gm. (30 gr.) in ten days; and sulfathiazoline, 2 Gm. (30 gr.) in ten days; all cured 100 per cent of chancroid cases totalling 200.

Importance of diagnosis of gonorrhea in women and in the control of this disease must not be overlooked. Jacoby<sup>18</sup> states that since inadequate sulfonamide therapy may cause a superficial disappearance of clinical symptoms of gonorrhea in women, all manifestations of the disease must be considered in diagnosis, including history of the patient and sex partners, positive smears or cultures, and past or present genitourinary symptoms. Discharge from the urethra or Skene's glands, or inflammation of Bartholin's glands or the cervix suggests gonococcal infection, particularly in conjunction with such subjective symptoms as pain in the lower abdomen, quadrant or back, disturbed menstrual function, or urinary frequency. The New York Department of Health recommends that 40 sulfathiazole tablets be prescribed at the first visit with the instruction that all are to be taken even if clinical symptoms disappear.

In the treatment of 500 prostitutes with chronic gonorrhea, Strauss, Hyman, and Grunstein<sup>19</sup> report a series of 488 prostitutes hospitalized for the treatment of gonorrhea, one-third of whom received 3 Gm. (45 gr.) *sulfathiazole* daily for ten days, one-third received 4 Gm. (60 gr.) daily for ten days, and one-third received 4 Gm. (60 gr.) daily for seven days; in the last two groups, the

percentage of apparent cures was raised without increase of toxic symptoms from the larger dose. At the end of the first sulfathiazole course, 441 (90.4 per cent) were negative by the minimum standard of 4 consecutive negative smears and 3 negative cultures; of 47 (9.6 per cent) failures, 42 became negative after the second course, consisting of *sulfathiazole* in 39 cases and *sulfapyridine* in 8; of the 5 remaining failures, 3 became negative after a sulfapyridine course, 1 after cauterization, and 1 after cervical coagulation. *Trichomonas vaginalis* vaginitis in 67 per cent, purulent discharge in over 67 per cent, or involvement of Skene's or Bartholin's glands, persisted despite sulfonamide therapy, even when gonococci were absent. Therapy had to be interrupted in one case in which a mild secondary anemia became severe after 4 Gm. (60 gr.) sulfapyridine for three days, and in another where hyperpyrexia, red throat, stiff neck, and abdominal and renal pain followed 16 Gm. (240 gr.) sulfathiazole. Slight nausea, headaches, dizziness, or transient rashes were occasional toxic symptoms, but the majority of the patients felt well and gained an average of 2.83 pounds.

In another report, Strauss, *et al.*,<sup>20</sup> report the observations on 65 bacteriologically positive gonorrhea patients; 64 became negative after taking 4 Gm. (60 gr.) a day sulfathiazole orally for seven days. *Trichomonas vaginalis* were found in the vaginal secretions of 66 per cent of the patients, and was unaffected by sulfonamide therapy. The clinical symptoms of gonorrhea were not alleviated in those patients. Of 58 patients who had had profuse mucopurulent discharge before treatment, 37 still had it when their cultures were negative. Although 85 per cent of the group showed clinical signs of gonorrhea when

examined repeatedly, only 30 per cent had shown such signs in a single gynecologic examination.

A minimum bacteriologic criterion of cure of gonorrhea in women is discussed by Lankford and Cooke.<sup>21</sup> Clinical subsidence of gonorrheal infection without elimination of the gonococcus, a latent gonorrhea, following sulfonamide therapy, was found in a group of patients at the John Sealy Hospital, Galveston, Texas. Each patient's record was studied to determine how many successive cultures were obtained during the time the patient exhibited evidence of infection, bacteriologic, clinical, or epidemiologic. Routine consisted of clinical and bacteriologic diagnosis of gonorrhea; treatment with *sulfapyridine*, *sulfathiazole*, or *fever therapy*, or the three in combination; culture and hematologic examination during treatment and bacteriologic tests at weekly intervals for two to four months after therapy. The number of successive cultures varied from two in many patients to 30 or more in a few. Some of these cases were sulfonamide-resistant; others represented treatment failures because of inadequate or irregular treatments. The authors found six or seven successive negative cultures, one or two postmenstrual, a reasonably safe minimum for discharge of treated cases. They suggest that the percentage of additional residual infections detected by more than six or seven tests is scarcely worth the added effort. Moreover, no practical number of cultures will detect all residual infections since the gonococcus may recede to the deep glandular crypts of the cervix, being expelled only at sporadic and infrequent intervals. A majority, but not 100 per cent, of infections will be detected by six to eight cultures. Negative smears had no value as bacteriologic tests of cure; artificial provocative measures,

chemicals and vaccines, have been practically abandoned as evidence of cure but the provocative effect of menstruation is well established.

In the review of the literature on the status of gonorrheal vaginitis in children, Welch<sup>22</sup> states that cultures are more accurate than smears in the diagnosis of gonococcal vaginitis, that intravaginal suppositories of natural *estrogens* or *stilbestrol* has been very satisfactory. Others<sup>23</sup> are of the same opinion. No toxic effects were noted.

Procedures recommended by the American Neisserian Medical Society<sup>24</sup> in the management of gonorrhea in general practice are as follows: Routine prophylaxis against gonorrhea should consist of utilization of a condom by the male; both hands and genitalia should be washed after its removal. Chemical prophylaxis should consist of thorough washing of the external genitalia and surrounding area with soap and water, the injection of 6 cc. (not more) of 10 per cent mild *protein silver solution* into the urethra and retention for five minutes. After excretion the surrounding area should be well anointed with 33.3 per cent *calomel ointment*, rubbed well into the skin, especially around the glans penis and the prepuce. *Oral sulfathiazole* before and after coitus may be effective, but the evidence is not yet conclusive. There is no satisfactory prophylactic treatment for women. Diagnosis is by laboratory smears with the Gram stain if a purulent discharge is present or by symptoms, such as gonorrheal urethritis, leukorrhea, cervical discharge, etc. Treatment should always be given when diagnosis is in doubt. General treatment consists of 1 Gm. (15 gr.) sulfathiazole orally q.i.d. after meals and at bedtime for five days and ten or more glasses of fluid daily. Immature girls should be

given 0.03 Gm. (0.5 gr.) per pound a day orally for seven days. Nausea, fever, or rash contraindicates further dosage. In resistant cases, the course may be repeated in three to four days or local treatment may be substituted; or fever therapy may be tried if available. In the male, local treatment may consist of daily irrigation with protein silver as above and *gentle prostatic stroking*. In the female, the treatment depends on the extent of infection. All cases should be examined periodically for three months after the disappearance of symptoms, and every attempt should be made to find the source of infection.

Prophylaxis at the present time merits discussion. E. C. Smith,<sup>25</sup> in a report on sex hygiene in the Navy, discusses prophylactic instruction in therapy which was begun in 1940 in the Newport Naval area. This interest was instrumental in reducing the incidence of venereal disease 80.27 to 36/1000 in the U. S. Navy, and in the Newport Naval area from 12 to 5/1000. Mechanical protection; chemical treatment, such as injection of 4 cc. of 2 per cent *Protargol* (strong silver solution) into the urethra and holding for five minutes, and application of *calomel ointment* to exposed parts; and chemotherapy, 4 Gm. (60 gr.) *sulfathiazole* orally in divided doses as late as 24 hours following exposure, are methods advocated.

Complete venereal prophylaxis with a sulfa-mercury compound is reported by K. P. A. Taylor.<sup>26</sup> No venereal disease followed 327 Navy prophylactic treatments with an emulsion containing *mercuric oxycyanide plus sulfathiazole* within two hours after exposure to prostitutes in a South Pacific area, where syphilis and gonorrhea were rife. In contrast, seven cases of venereal disease, including gonorrhea and chancroid, occurred after 287 prophylactic treat-

ments with *Protargol* and calomel ointment under the same conditions. The mercuric oxycyanide-sulfathiazole preparation caused no toxic reactions or unusual irritation, and was nonstaining. Between 1932 and 1938, Taylor found an aqueous solution of *mercury oxycyanide* alone to be effective in 223 prophylactic treatments in private practice. Between 1938 and 1942, a solution containing mercury oxycyanide plus sulfanilamide was used in 202 cases, and in 1942 an emulsion was adopted which could be placed in individual tubes or kits and which contained 0.1 Gm. (2 gr.) mercuric oxycyanide, 5 Gm. (75 gr.) sulfathiazole, 5 Gm. (75 gr.) cornstarch, and distilled water to 100 Gm. This emulsion is stable for over three months, except for a slight color change.

Prophylaxis with sulfathiazole in venereal disease is discussed in the literature in the report by Arthur and Dermon.<sup>27</sup> In 42 of 259 men (384 exposures) given routine army venereal disease prophylaxis, consisting of washing with soap and water, mild *mercurous chloride ointment*, and a urethral injection of mild protein solution, venereal disease developed: 9 cases of primary syphilis, 15 of gonorrhea, and 18 of chancroid. In 152 (199 exposures) receiving sulfathiazole prophylaxis (3 Gm., 2 Gm., and 1 Gm. [45 gr., 30 gr., and 15 gr.], after breakfast, dinner, and supper, respectively), no gonorrhea, 1 chancroid, and 5 cases of syphilis developed. Of the latter, 1 showed a faint roseola, and the other 4 had positive serological tests, with no lesions. Thus the rate of infection in those receiving sulfonamide therapy was 30/1000 as against 109/1000 in routine prophylaxis.

**Fever Therapy**—One must not overlook in the treatment of gonorrhea a recent addition in our treatment armamentarium; namely, fever therapy. This



method, while not universally in use, has proved to be of value in sulfa-resistant cases of gonorrhea. Tayloe,<sup>28</sup> in a recent report, combines *sulfonamide* and *artificial fever therapy* successfully to cure 45 out of 51 cases of sulfa-resistant gonococci infection, including two severe cases of unilateral gonorrheal ophthalmia, and two of severe gonorrheal arthritis.

**Penicillin**—Penicillin, in cases resistant to all forms of accepted therapy in gonorrheal infections has been used with extremely gratifying results. Unlike the sulfonamides, the bacteriostatic powers (unpublished report)<sup>29</sup> of penicillin are not inhibited by para-aminobenzoic acid or by the products of tissue autolysis, by peptone, by purulent exudates, blood or serum, or by the number of bacteria to be inhibited. This last fact causes *penicillin* to act beneficially in heavily infected wounds and when there is much purulent discharge. Penicillin, therefore, is a very excellent therapeutic agent in the treatment of resistant cases of gonorrhea and is especially beneficial in those cases of gonorrhea which, because of poor drainage and the nature of the lining of the mucous membranes of the lower urinary tract, do not respond to accepted methods of treatment. Penicillin-resistant strains of staphylococci, streptococci, and pneumococci have been grown but the bacteria lose their virulence and undergo morphologic and metabolic changes which appear to be permanent. It is reported that in some patients organisms isolated before institution of treatment were less resistant to penicillin than those isolated late in treatment. In certain subjects, therefore, penicillin therapy may result in the development of resistant strains. This phenomenon explains many of the therapeutic failures with the sulfonamide drugs and the same may be expected to

hold true in the case of penicillin. It is advisable, therefore, to give sufficiently large amounts of the drugs early in the course of treatment to insure the bactericidal effects on the microorganisms and prevent the transformation into resistant forms by the exposure to sublethal amounts.

Unpublished data collected by the Committee on Chemotherapeutics and Other Agents of the National Research Council record the preliminary clinical trials of the sodium salt of penicillin in 264 cases. The results have completely upheld the promise contained in earlier reports of English investigators.

Cases of gonorrhea resistant to all forms of therapy have responded to penicillin. The Mayo Clinic<sup>30</sup> reports good results as well as the National Research Council in sulfonamide-resistant cases of gonorrhea, and recently Mahoney and his group of workers at Staten Island report similar promising results. The United States Naval Hospital at Philadelphia have been very fortunate in being chosen to institute treatment in resistant cases of gonorrhea. Excellent results in 42 cases can be reported at this time, the men being sent back to duty in an amazingly short period of time. The most outstanding case is a young man who was admitted with an acute gonorrheal arthritis complicated by high temperature, and was also extremely ill. After three days of therapy with penicillin he was completely relieved of all symptoms and after five negative cultures from the prostate and urethra returned to duty.

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## SYPHILIS

The statement made by Stokes that syphilis is insidious, ubiquitous, and disastrous becomes more evident at this time. An analysis of 1,895,778 serologic



reports of men between the ages of 21 and 35 were examined under the Selective Training and Service Act of 1940, and reported by Vonderlehr and Usilton.<sup>31</sup> Syphilis prevalence rates per 1000 were 17.4 for white selectees, and 272 for Negroes, and 45.3 for both combined, according to blood tests.

The most outstanding contribution in this year's literature is the rapid method treatment of syphilis. Neilson and Gabby<sup>32</sup> state that of 75 per cent of 500 patients treated with the *massive-dose arsenotherapy* and followed up five months or more later, 1.2 per cent were still seropositive, 89.6 per cent were entirely negative or nearly so, 8 per cent suffered relapses, 1.2 per cent were reinfected, and 3 had died. Patients receiving *mapharsen* alone became seronegative in an average of 4.37 months, those receiving *mapharsen plus bismuth* in an average of 2.82 months. Those with primary syphilis and seronegative became positive and then negative in less than a month, those seropositive required nearly four months, and those with secondary syphilis required over five months before becoming seronegative.

Another paper of interest is the one by Bowman and Huber,<sup>33</sup> who treated 30 patients who were or became pregnant during treatment with massive arsenotherapy. They report 27 babies living and seronegative.

Eagle and Hogan<sup>34</sup> report an experimental evaluation of intensive methods for the treatment of early syphilis. In the various intensive schedules which have been used for the treatment of early syphilis in man, the dose of *mapharsen* which has "cured" a satisfactory proportion of cases has been largely independent of the frequency of injection or the duration of treatment. This curative dose has been 20 to 30 mg. per Kg., or

approximately 1500 mg. in a man weighing 60 Kg. The relative constancy of the total curative dose is in accord with the animal data previously reported. The margin of safety provided by any intensive procedure is therefore primarily a function of its toxicity. That margin of safety, calculated from the animal data on toxicity, has varied from three to ten in the treatment schedules which have been used in man. The observed incidence of toxic reactions and of deaths has been in complete accord with, and predictable from, this calculated margin. Thus, the administration of 1200 mg. in a five-day intravenous drip, with a safety factor of 3.0, has resulted in a mortality of 1:200, and serious toxic reactions in 1 in every 100 patients treated. Standard weekly practice, with a safety factor of 10, has a mortality of less than 1:3000; and treatment schedules with intermediate factors of safety have resulted in a correspondingly intermediate incidence of toxic reactions and deaths. It is estimated that a margin of safety of 6 to 8 is necessary to reduce the mortality of antisyphilitic treatment to less than 1:1000. With the drugs and methods now available, no treatment completed in 20 days or less meets that reasonable requirement, no matter how the injections are given. That margin of safety would, however, be provided by giving the total curative dose in triweekly injections for seven weeks, daily injections for approximately six weeks, or multiple daily injections, or an intravenous drip for an estimated period of 4 to 6 weeks. The triweekly schedule has the important advantage of permitting treatment to be carried out on an ambulant basis in the average clinic. This method is now under study in 80 coöperating clinics. The size of the individual dose has been fixed at approximately 1 mg. per Kg., with a maximum

of 80 mg. and a minimum of 40 mg. The duration of treatment has been varied from 6 to 12 weeks. The minimum effective total dosage, the advisability of concurrent injections of bismuth, and the applicability of the procedure to the treatment of latent syphilis are some of the factors under consideration.

Of interest at the present time and reported by Favorite<sup>35</sup> is the fact that false positive reactions by the Kolmer, Kahn, or Mazzini tests for syphilis were obtained in 24 of 202 subjects (11.8 per cent) 10 to 57 days after smallpox vaccinations. Retesting every two weeks showed a gradual decrease in the intensity of the reaction until all were negative after 120 days.

### PENILE LESIONS

An excellent discourse on this subject is given by Greenblatt<sup>36</sup> in *Venereal Disease Information Supplement No. 19*. Granuloma inguinale, lymphogranuloma venereum, and chancroid are discussed. Lymphogranuloma venereum is a widespread, communicable disease, usually acquired venereally. It is caused by a specific filtrable agent which can bring about infection in certain experimental animals. The infective agent usually gains entrance to the body through the skin or mucous membranes of the external genitalia or anorectal region. Usually, although not always, a small, transitory herpetiform lesion is produced at the point of entrance. It may also gain entrance through the mouth or conjunctiva and rarely through other extragenital tissues. The incubation period is not firmly established but is considered to be from one to three weeks after exposure. The disease affects all races but shows greater incidence among the Negroes in the United States. A higher incidence has been reported in males

than in females although this may be apparent rather than real. The disease occurs more frequently within the age limits of greater sexual activity. Surveys indicate that a comparatively high percentage of those sexually promiscuous have been infected. It is probable that the disease is much more common than is generally supposed, and perhaps more benign, with a natural tendency to spontaneous cure.

Other names, which are chiefly anatomical or descriptive in character, are frequently found in the literature. These include: Tropical bubo; strumous or scrofulous bubo; lymphogranuloma inguinale or poradenitis; venereal lymphogranuloma, esthiomene; nontuberculous granulomatous lymphadenitis; lymphopathia venereum, lupus vulvae; chronic elephantiasis, with vulvar ulceration; and inflammatory stricture of the rectum. To further confuse the nomenclature, terms such as "Fourth Venereal Disease," "A Sixth Venereal Disease," and Nicolas-Favre disease have been used.

**Treatment** — *Sulfonamides* in adequate dosage both orally and locally to the lesions appear to be the treatment of choice. Particularly in acute bubo or systemic infections in the chronic stage, as in rectal stricture or in elephantiasis vulvae, little effect is noted. In cases of ulcerative colitis and rectitis due to the virus of this disease, oral *sulfaguanidine* and *succinylsulfathiazole* enemas are of some value.

Fluctuant buboes should never be incised, but aspirated. Satisfactory results have been ascribed to the biweekly injections of ascending doses of *Frei antigen* from 0.05 to 1 cc. or 0.1 to 0.2 cc. over a period of months. These are given subcutaneously. It can, however, be used intravenously at intervals of four to seven days. Convalescent blood from patients with this disease has also been suggested.

## CHANCROID

Chancroid is commonly seen in the service and occurs endemically in the Mediterranean area, especially in Italy and Morocco, as well as in subtropical and tropical countries. In the United States Navy for the year 1929 there were 3652 cases (an incidence of 31.11 per 1000 admissions). The disease begins as a vesicopustule which breaks down rapidly, leaving a sharply circumscribed, crater-like ulceration which is moist and covered with necrotic grayish exudate. The lesion may be single or multiple, which may occur in the male on the preputial orifice, internal surface of prepuce, the frenum, the shaft of the penis, and the anal orifice; in the female, on the labia, clitoris, fourchette, vestibule, anus, and cervix. Chancroidal urethritis, as well as intraurethral chancroid, has been observed. Diagnosis is made by the recoveries of the *Haemophilus ducreyi* from the lesion or by the exudate stained with the Gram, Unna-Pappenheim, Wright, or Giemsa stain, or by means of culture from the aspirated pus from the bubo, or by the interdermal reaction similar to the Frei test.

**Treatment**—The sulfonamides (*sulfanilamide*, *sulfathiazole*, or *sulfadiazine*) are specific in the therapy of chancroid. Sulfathiazole is the drug of choice; the administration of 2 to 4 Gm. (30 to 60 gr.) in divided doses for 7 days is curative in 7 to 12 days in most cases. Local applications of sulfathiazole powder or sulfathiazole ointment are not nearly as efficacious if used alone, but may be used as an adjunct to peroral therapy or where there is indication for withdrawal of peroral administration of the drug because of toxicity. Recently the author has applied red blood cell paste to the lesions with promising results.

## GRANULOMA INGUINALE

Granuloma inguinale is a granulomatous process which usually occupies the inguinal region. It is a mildly contagious, chronic, and progressive auto-inoculable disease involving skin and corium and occasionally the lymphatics. The well known proclivity of the disease for the external genitalia has earned for it a place in the category of the venereal diseases. Its venereal origin, however, has never been absolutely proved. Granuloma inguinale has been known by a multitude of names, such as ulcerating granuloma, granuloma pudendi tropicum, sclerosing granuloma, granuloma inguinale tropicum, granuloma contagiosa, chronic venereal sores, and granuloma venereum. Although granuloma inguinale is possibly not the best name, for it implies that the disease is confined to the inguinal region, nevertheless prolonged and generalized usage has made it the term of choice.

The etiologic agent of granuloma inguinale is the Donovan body. Donovan bodies are probably protozoans and are not culturable *in vitro* by methods used to propagate fastidious bacteria, Rickettsial bodies, and viruses. The disease has been reproduced in humans by inoculation of aspirated pus from pseudobuboes of granuloma inguinale which contained no other organisms than Donovan bodies. These organisms were recovered in abundance, to the exclusion of other organs, from the experimental lesions that were induced. Attempts to reproduce the disease in experimental animals such as the dog, rabbit, guinea pig, rat, mouse, and hamster have met with failure. The Donovan bodies are strictly tissue parasites of man. Little is known about the incubation period of granuloma inguinale. Granuloma inguinale is considered generally as a venereal dis-

case, and the consensus is that it is acquired by coitus. The majority of cases observed have ranged from 20 to 40 years of age. This corresponds to the period of greatest sexual activity. An analysis of the sexual incidence of granuloma inguinale reveals that there are nearly twice as many males as females with this disease. Early reports localized the disease to India and such tropical regions as British Guiana and New Guinea. Isolated reports soon established the fact that the disease was encountered in temperate zones, usually, however, in persons who had traveled in the Tropics. The disease makes its appearance insidiously, without premonitory symptoms or constitutional upset. The disease starts as a vesicle, papule, or nodule. The lesions show very little tendency to heal; they spread by continuity or contiguity. Extension is often slow, showing only insidious progress. Occasionally, the spread is more rapid, and there is a predilection for moist contact surfaces particularly in the cruro-scrotal folds. Daughter lesions frequently develop near the larger lesions. These coalesce after a time to form extensive ulcerative processes. The advancing border of the lesion has characteristic rolled edges, the granulation tissue piling over onto the bordering epithelial surface. Most of the extragenital lesions are secondary to pudendal lesions although in a few instances purely extragenital lesions have been described. Extragenital lesions occur in about 6 per cent of all cases of granuloma inguinale.

**Treatment — Chemotherapy** — The effectiveness of chemotherapy decreases in direct proportion to the chronicity of the lesions. Early granuloma inguinale responds rapidly to therapy with various antimony preparations. *Tartar emetic* (1 per cent) may be given intravenously in ascending doses beginning with 1 cc.

(16 minims) and increasing the dose by 1 cc. (16 minims) until a dose of 10 cc. (160 minims) is reached. It is administered every two or three days. When the maximum is reached, the dosage is decreased by 1 cc. (16 minims) in descending strength until it is reduced to the initial dosage. After a two-week rest period, medication is again started. Toxic manifestations, such as joint pains, sore gums, anorexia, nausea, and vomiting, are often encountered with tartar emetic. Freshly prepared 1 per cent solutions are said to be more effective than stock ampules.

**Fuadin** (Winthrop) has proved to be superior to tartar emetic. It is more convenient to administer, and toxic reactions are seldom encountered. The solutions are stable and are available in 1.5, 3, and 5 cc. (24, 48, and 80 minims) ampules. The initial dosage of Fuadin is 1.5 or 3 cc. (24 or 48 minims) intramuscularly. The dosage is then raised to 5 cc. 80 minims) and given three times per week.

**Anthiomaline** (Merck) is another stable and useful preparation that yields good results in a high percentage of cases. It is available in 3-cc. (48-minim) ampules and is administered intramuscularly three times per week. When lesions remain refractory to treatment with one preparation, a change to another antimony compound is recommended. Usually definite improvement in the lesions may be noted within four to six weeks. Either Fuadin or Anthiomaline should be continued until healing is complete. Medication should then be administered at weekly intervals for a period of six months if recurrences are to be avoided. Cure may be obtained in practically every case of granuloma inguinale when the diagnosis is made within the first six months of the infection.

## CONCLUSION

It becomes evident from the preceding pages that the present emergency has made us more conscious of the venereal disease problem confronting us. It might be appropriate to state that it will be well to standardize the treatment of venereal diseases and alleviate the present state of confusion, especially in the treatment of gonorrhea. Such standardization must not be inflexible, for each case is an individual problem. A confusing scheme of treatment only tends to cause prolongation of the disease. The pathology that we see in most instances, especially in gonorrhea, is man-made. In concluding, we can say that we are fortunate in that we have available therapeutic agents, such as the sulfonamides, fever therapy, penicillin, and a great interest of those who guide our destinies, to help us fight this great scourge which affects our fighting capacity in this global war.

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